Hackensack Meridian Health

Standard Operating Procedures for Human Research Protection Program (HRPP)

Version 6.8, May 6, 2022

Due to the highly integrated and cooperative relationship with Hackensack Meridian Health, with the approval of the Hackensack Meridian School of Medicine (HMSOM) Board of Governors, the HMSOM has adopted Hackensack Meridian Health's Human Research Protections Program (HRPP) Standard Operating Procedures (SOPs) and all associated documents including the conflict of interest in research and the conflict of interest reporting form.

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1 Human Research Protection Program

The Hackensack Meridian Health network fosters a research environment that promotes the respect for the rights and welfare of individuals recruited for, or participating in, research conducted by or under the auspices of the Organization. The review and conduct of research, actions by the Organization 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*** (referred to as the *Belmont Report*). The actions of Organization will also conform to all applicable federal, state, and local laws and regulations. In order to fulfill this policy, the Organization has established a Human Research Protection Program (HRPP). The Hackensack Meridian Health (HMH) 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. The research may be externally funded, funded from internal sources, or conducted without direct funding.

1.1 Mission

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;
- Provide guidance and support to the research community in the conduct of research with human subjects;
- Assist the research community in ensuring compliance with relevant regulations;
- To provide timely and high quality education, review and monitoring of human research projects; and
- To facilitate excellence in human subjects research.

The HRPP includes mechanisms to:

- Monitor, evaluate and continually improve the protection of human research participants
- Dedicate sufficient resources to facilitate excellence and integrity in human research
- 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 Organizational Authority

The HMH Meridian Health Human Research Protection Program operates under the authority of the Organization policy "Human Research Protection Program (HRPP)" adopted on January 31, 2015. 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 HMH. The HRPP Policy and these operating procedures are made available to all HMH investigators and research staff and are posted on the HMH website and in the Administrative Policy Manual.

1.3 Definitions

Common Rule. The Common Rule refers to the "Federal Policy for the Protection of Human Subjects" adopted by a number of federal agencies. Although the Common Rule is codified by each agency separately, the text is identical to DHHS regulations in 45 CFR 46 Subpart A. For the purposes of this document, references to the Common Rule will cite the DHHS regulations.

Clinical Trial. Per the Common Rule and NIH Policy, clinical trial means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes. FDA regulations refer to "clinical investigations" (see definition of "research" below).

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

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

Research. The Common Rule defines research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalized knowledge. Activities which meet this definition constitute research whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities. For purposes of this part [the Common Rule], the following activities are deemed not to be research: (1) Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected. (2) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness

and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters). (3) Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes. (4) Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions. [45 CFR 46.102(l)]

For the purposes of this policy, a **"systematic investigation"** is an activity that involves a prospective study plan that incorporates data collection, either quantitative or qualitative, and data analysis to answer a study question. Investigations designed to develop or contribute to **generalizable knowledge** are those designed to draw general conclusions (i.e., knowledge gained from a study may be applied to populations outside of the specific study population), inform policy, or generalize findings.

The FDA has defined "research" as being synonymous with the term "clinical investigation." A clinical investigation, as defined by FDA regulations, means 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 Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the Federal Food, Drug, and Cosmetic 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 terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations. [21 CFR 50.3(c), 21 CFR 56.102(c)]

Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) of the Federal Food, Drug, and Cosmetic Act means any use of a drug other than the use of an approved drug in the course of medical practice. [21 CFR 312.3(b)]

Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 520(g) of the Federal Food, Drug, and Cosmetic Act means any activity that evaluates the safety or effectiveness of a device. [21 CFR 812.2(a)]

Any activity in which results are being submitted to or held for inspection by FDA as part of an application for a research or marketing permit is considered to be FDA-regulated research. [21 CFR 50.3(c), 21 CFR 56.102(c)]

Human Subject. A human subject as defined by the Common Rule is a living individual about whom an investigator conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. [45 CFR 46.102(e)(1)]

- I**ntervention** means both physical procedures by which information or biospecimens are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. [45 CFR 46.102(e)(2)]
- **Interaction** means communication or interpersonal contact between investigator and subject. [45 CFR 46.102(e)(3)]
- **Private information** 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). [45 CFR 46.102(e)(4)]

- **Identifiable private information** means private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information. [45 CFR 46.102(e)(5)]. Note: This definition is within the Common Rule. For a discussion of identifiability under HIPAA, please see Section 23.
- **Identifiable biospecimen** means a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen [45 CFR 46.102(e)(6)]

For research covered by FDA regulations, human subject means an individual who is or becomes a participant in a clinical investigation, 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 also includes any individual on whose specimen an investigational device is used or tested or used as a control (regardless of whether the specimens are identifiable). [21 CFR 50.3(g), 21 CFR 312.3(b), 21 CFR 812.3(p)]

Test Article. The FDA defines *"Test article"* as meaning any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act [42 U.S.C. 262 and 263b-263n]. [21 CFR 50.3(j)]

Test articles covered under the FDA regulations include, but are not limited to:

1. **Human drugs** – The primary intended use of the product is achieved through chemical action or by being metabolized by the body. A drug is defined as a substance recognized by an official pharmacopoeia or formulary; a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; a substance (other than food) intended to affect the structure or any function of the body; a substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device. Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process.) *http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm*

2. **Medical Devices** - A device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them; intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051512.htm

3. **Biological Products** - include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available.
http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm

4. **Dietary Supplements** – A dietary supplement is a product taken by mouth that is intended to supplement the diet and that contains one or more "dietary ingredients." The "dietary ingredients" in these products may include vitamins, minerals, herbs or other botanicals, amino acids, and other substances found in the human diet, such as enzymes. When a dietary supplement meets the definition of drug, it is regulated as such.

5. **Medical Foods** – A medical food, as defined in section 5(b) of the Orphan Drug Act (21 U.S.C. 360ee (b) (3)), is a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.

6. **Mobile Medical Apps** - Mobile apps are software programs that run on smartphones and other mobile communication devices. They can also be accessories that attach to a smartphone or other mobile communication devices, or a combination of accessories and software. Mobile medical apps are medical devices that are mobile apps, meet the definition of a medical device and are an accessory to a regulated medical device or transform a mobile platform into a regulated medical device.

7. **Radioactive Drugs** – The term radioactive drug means any substance defined as a drug which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance but does not include

drugs such as carbon-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides. The term "radioactive drug" includes "radioactive biological product".

8. **Food Additives** - A food additive is defined in Section 201(s) of the FD&C Act as any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristic of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use); if such substance is not Generally Recognized As Safe (GRAS) or sanctioned prior to 1958 or otherwise excluded from the definition of food *additives.*
   http://www.fda.gov/Food/IngredientsPackagingLabeling/Definitions/default.htm
9. **Color Additives** - A color additive is any dye, pigment or substance which when added or applied to a food, drug or cosmetic, or to the human body, is capable (alone or through reactions with other substances) of imparting color. Color additives for use in food, drugs, and cosmetics require premarket approval. Color additives for use in or on a medical device are subject to premarket approval, if the color additive comes in direct contact with the body for a significant period of time. Radiation-Emitting Electronic Products a radiation-emitting electronic product as any electrically-powered product that can emit any form of radiation on the electromagnetic spectrum. These include a variety of medical and non-medical products such as mammography devices, magnetic resonance imaging (MRI) devices, laser toys, laser pointers, liquid crystal displays (LCDs), and light emitting diodes (LEDs).

1.4 Ethical Principles

Hackensack Meridian Health is committed to conducting research with the highest regard for the welfare of human subjects. With the exception of transnational research, where consideration of alternative ethical principles may apply (see Section 25), HMH 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:

1) **Respect for Persons**, which involves obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations.
2) **Beneficence**, which involves ensuring that possible benefits are maximized and possible risks are minimized to all human subjects.
3) **Justice**, which involves the equitable selection of subjects.

HMH Human Research Protection Program (HRPP), in partnership with its research community, including researchers and research staff, IRB members and chairs, IRB staff, the organizational official, employees, faculty, and students, 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 program is responsible for ensuring compliance with federal regulations, state law and organizational policies. All human subjects research at HMH is conducted in accordance with the policy and regulations found in the Common Rule and 21 CFR 50 and 56. The actions of HMH will also conform to all other applicable federal, state, and local laws and regulations such as Department of Defense (DoD) and Family Educational Rights and Privacy Act (FERFPA.

Research supported by the Department of Defense (DoD) is reviewed and conducted in compliance with part 219 of title 32 CFR, part 980 of title 10 USC, applicable parts of title 21 CFR (50, 56, 312, 600, 812), DoD Instruction 3216.02, DoD Directive 3210.07, and applicable additional requirements from respective DoD component(s). See Section 25.10 for additional DOD requirements.

Research involving the use of Protected Health Information is reviewed and conducted in accordance with the Health Insurance Portability and Accountability Act (HIPAA), 45 CFR Part 160, 162, and 164.

Research conducted or supported by the U.S. **Department of Education (ED)** is subject to the Common Rule with regulations published at 34 CFR 97. In addition to the Common Rule, human subjects research involving education records conducted at institutions receiving ED funding must comply with additional requirements, including the Family Educational Rights and Privacy Act (FERPA) (34 CFR 99) and the Protection of Pupil Rights Amendment (PPRA) (34 CFR 98). Investigators should consult these regulations and resources provided by ED when developing their research protocol. The IRB will evaluate the research in accordance with these regulations when applicable. See the Special Topics section of this manual for more information.

Research involving the use of student educational records is reviewed and conducted in accordance with the Family Educational Rights and Privacy Act (FERPA), 34 CFR Part 99.

1.5.1 Management of pre-existing studies once the revised Common Rule goes into effect

For research subject to the Common Rule (whether due to support or organization policy) the following outlines when the old rule or the revised rule will apply to research conducted at HMH.

A. **Research subject to the old rule (pre-2018 requirements).** The old rule will apply to the following studies, unless a study is transitioned to comply with the revised rule as described below.
   - All studies initially approved, waived under .101(i), or determined exempt before January 21, 2019 will be subject to the old rule through the close of study.

B. **Research transitioned between July 19, 2018 and January 20, 2019 to adopt a burden-reducing provision described in the revised rule .101(l)(4).** Studies described in Section

A may be transitioned to comply with any of the three burden-reducing provisions described in the revised rule.

C. Research subject to the revised rule (2018 requirements). The revised rule will apply to the following studies.

- All studies initially approved, waived under .101(i), or determined exempt on or after January 21, 2019 will be subject to the revised rule.
- All studies described in section B that were transitioned to adopt a burden-reducing provision between July 19, 2018 and January 20, 2019 must comply will all other applicable provisions of the revised rule beginning on January 21, 2019.
- On or after January 21, 2019, Institutions have the flexibility to transition individual studies described in section A and agree to comply with the new rule if they so choose. The study must comply with the revised rule on the date the determination to transition is documented.

1.6 International Conference on Harmonization-Good Clinical Practice (ICH-GCP)

HMH voluntarily applies the International Conference on Harmonization ("ICH") Good Clinical Practices ("GCP") Guidelines (sometimes referred to as "ICH-GCP" or "E6") to prospective and retrospective human subjects research conducted under its IRB. In general, HMH applies the ICH-GCP guidelines only to the extent that they are compatible with FDA and DHHS regulations.

1.7 Federalwide Assurance (FWA)

The federal regulations require that federally-funded human subject research only be conducted at facilities covered by a Federalwide Assurance (FWA) approved by the DHHS Office for Human Research Protections (OHRP). An FWA is an organization's assurance to the federal government that human subject research conducted at that site is in compliance with federal regulations pertaining to the protection of human subjects. The FWA designates the Institutional Review Board that will review and oversee the research, specifies the ethical principles under which the research will be conducted, and names the individuals who will be responsible for the proper conduct of the research.

HMH has an OHRP-approved Federalwide Assurance (FWA number 00000331) and has designated 4 IRB(s) to facilitate the conduct of research. HMH Institutional Review Board (HMH IRB) # 1 reviews all investigator-initiated research and also serves the function as the Privacy Board for the northern network hospitals, HMH Institutional Review Board (HMH IRB) # 2 reviews all investigator-initiated research and also serves the function as the Privacy Board for the southern network hospitals. Sponsored research is typically reviewed by an external IRB, including but not limited to Western Institutional Review Board (WIRB), Advarra IRB, or an external Institutional IRB. NCI Cooperative Institutional Review Board (CIRB) serves as the IRB of record for cooperative research (registered as 00000781/00009430/00004296/00010018) to review all human research plans.

In its FWA, HMH has opted to limit the application of the FWA to non-exempt human subject research conducted or supported by DHHS or federal agencies that have

The HHS registration system database can be used to verify the status of HMH's FWA, IORG, and IRB registration.

HMH's Federal Registration Numbers	
FWA	00000331
IORG	0000713
IRB Registration	IRB00011536

1.8 Research Under the Auspices of the Organization

Research under the auspices of the organization includes research conducted at this organization, conducted by or under the direction of any employee or agent of this organization (including students) in connection with his or her organizational responsibilities and at an HMH location, conducted by or under the direction of any employee or agent of this organization using any property or facility of this organization, or involving the use of this organization's non-public information to identify, contact, or study human subjects. A Department Chair with departmental signatory responsibilities for research may request an exception to this policy (ex. An HMH-employed physician seeking to include their independent practice location as a research site) for consideration by the Institutional Official.

Employee or Agent. For the purposes of this document, *employees or agents* refers to individuals who: (1) act on behalf of the organization; (2) exercise organizational authority or responsibility; or (3) perform organizationally designated activities. "Employees and agents" can include staff, students, contractors, and volunteers, among others, regardless of whether the individual is receiving compensation.

Engagement. The Department of Health and Human Services (DHHS) regulations [45 CFR 46.103[a]] require that an institution "engaged" in human subject research conducted or supported by a Federal Department or Agency provide the Office for Human Research Protection (OHRP) with a satisfactory assurance of compliance with the DHHS regulations, unless the research is exempt under 45 CFR 46.101(b). *"In general, an institution is considered engaged in a particular non-exempt human subjects research project when its employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research."* In general, institutions that receive an award through a grant, contract, or cooperative agreement directly from DHHS for the non-exempt human subjects research (i.e. awardee institutions), are also considered engaged in research even where all activities involving human subjects are carried out by employees or agents of another institution.

FDA regulations are oriented to the responsibilities of IRBs, investigators, and sponsors as opposed to institutions. In general, FDA-regulated research conducted in HMH's facilities or by HMH's Principal or Sub-Investigators (as defined on the FDA 1572 or delegation of responsibilities log) requires review by an HMH- designated IRB. Exceptions to this requirement may be granted on a case-by-case basis (e.g., when HMH's involvement in the research is limited to the provision of a common diagnostic procedure and associated reading or analysis).

An IRB Chair or Vice Chair, with the assistance of the RIO Manager and legal counsel as needed, will determine whether HMH is engaged in a particular research study. Investigators and other institutions may not independently determine HMH's engagement.

When HMH is engaged in research, the Institutional Official may choose to enter into an agreement to cede review to an external IRB.

For additional information on determining engagement please refer to Guidance on Engagement on Institutions in Human Subjects Research, *http://www.hhs.gov/ohrp/policy/engage08.html*

1.9 Written policies and procedures

HMH Standard Operating Policies and Procedures for Human Research Protection detail the policies and regulations governing research with human subjects and the requirements for submitting research proposals for review by the Hackensack IRB or one of the affiliated IRB's of record. This is not a static document. The policies and procedures are annually reviewed and revised by the Institutional Official, Director of the HRPP, Counsel RIO Manager, and IRB Administrator. The Institutional Official and Director of the HRPP will approve all revisions of the policies and procedures.

The Institutional Official, through the Office of Research Administration, will keep the Organization 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 Office of Research Administration and IRB websites, and in the administrative policy manual. Changes to the policies and procedures are communicated to investigators and research staff, and IRB members and IRB staff through training sessions and announcements from the electronic research submission system.

1.10 HMH HRPP Structure

The HRPP consists of various individuals and committees that are responsible for maintaining the Human Research Protection Program objectives. This consists of Chief Research Officer and Institutional Official, VP of Research Operations and Regulatory Affairs, the Director of the HRPP, the Chief Compliance Officer, the RIO Manager and staff, the IRB(s), the Institutional Biosafety Committee (e.g, for gene transfer research), Radiation Safety Committee, Radioactive Drug Research Committee, Conflict of Interest Committee, the Office of Research

Administration, Legal Counsel, investigators, research staff, health and safety staff (e.g., Biosafety Officer, Radiation Safety Officer) and research pharmacy staff. The objective of this system is to assist the organization 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 human subject protections:

1.10.1 Institutional Official

The ultimate responsibility of the HRPP resides with the **Institutional Official (IO)** of the research program. The IO is legally authorized to represent Hackensack Meridian Health. The IO is the signatory of the FWA and assumes the obligations of the FWA. At HMH the President, Northern Region and Chief Research Officer is the Institutional Official. The IO is responsible for ensuring that the HMH's HRPP and IRB(s) have the resources and support necessary to comply with all organizational policies, laws, and regulations that govern human subject research. Such resources include, but are not limited to:

- Staffing commensurate with the size and complexity of the research program
- Appropriate office space, equipment, materials, and technology;
- Resources for the production, maintenance, and secure storage of HRPP and IRB records;
- Resources for auditing and other compliance activities and investigation of non-compliance;
- Access to legal counsel;
- Supporting educational opportunities related to human research protections for IRB members, relevant administrative staff, and all members of the research team.
- Support for evaluation of Conflict of Interest; and
- Support for Community Outreach.

The IO conducts and documents an annual review of HRPP and IRB function, requirements, and resources and makes adjustments as needed. The adequacy of personnel and non-personnel resources of the HRPP is assessed on an annual basis by the Director of the HRPP, the RIO Manager, and the IRB Administrator, and are reviewed and approved by the IO. The resources provided for the IRB and the HRPP will be reviewed during the annual budget review process.

The IO is also responsible for:

- Fostering, supporting and maintaining an organizational culture that supports the ethical conduct of all research involving human subjects and the adherence to regulations and organizational policies;

- Ensuring that the IRB functions independently by, among other mechanisms, being directly accessible to the IRB Chair(s) and members if they experience undue influence or if they have concerns about the function of the IRB;
- Oversight of the Institutional Review Board (IRB);
- Oversight over the conduct of research conducted by all HMH investigators;
- Assuring the IRB members are appropriately knowledgeable to review research in accordance with ethical standards and applicable regulations;
- Assuring that all investigators are appropriately knowledgeable to conduct research in accordance with ethical standards and applicable regulations; and
- Oversight of the development and implementation of an educational plan for IRB members, staff and investigators.

The IO must complete the training on human research protections available from Collaborative Institutional Training Initiative (CITI). The HRPP Office will provide on-going continuing education for the IO concerning human research protections.

The designated IO is made known to employees of the organization and is accessible by phone, email, in person or other methods of communication. The IRB Chair, Vice Chair and Director of Human Research Protection Program have access to the IO for any concerns or issues related to the HRPP.

In the performance of these duties, the IO has the authority to delegate such activities as may be necessary in order to effectively administer the program. However, the IO is ultimately responsible and is expected to be knowledgeable about all human subject protections responsibilities at the organization.

1.10.2 Vice President of Research Operations and Regulatory Affairs

The Vice President is responsible for the financial viability and continued growth of the research enterprise and the oversight of the HRPP/research regulatory affairs

The role of the VP is also to promote and strengthen a research culture, expanding the cohort of faculty actively engaged in research and fostering enthusiasm, excitement and motivation for research. The VP is also responsible for community engagement in research as measured by patient enrollment, legal, and regulatory compliance.

1.10.3 Director of Human Research Protection Program

The VP of Research and Regulatory Affairs delegates oversight of the HRPP to the Director of Human Research Protection Program, who 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 the administration of the IRB.

2. Advising the IO on key matters regarding research at HMH and its affiliates.
3. Implementing the organization's HRPP policies and procedures.
4. Submitting, implementing and maintaining an approved FWA through the IO and the Department of Health and Human Services Office of Human Research Protection (OHRP).
5. Assisting investigators in their efforts to carry out Organization's research mission.
6. Developing and implementing needed improvements and ensuring follow-up of actions, as appropriate, for the purpose of managing risk in the research program.
7. 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.
8. Serving as the primary contact at HMH for the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services, the Food & Drug Administration (FDA) and other federal regulatory agencies.
9. Day-to-day responsibility for the operation of the HRPP office, including supervision of HRPP and IRB staff.
10. Responding to questions regarding the protection of human subjects.
12. Working closely with the Chair of the IRB on the development of policy and procedures, as well as organizing and documenting the review process.

1.10.4 HRPP/Research Integrity Staff

In addition to the leadership structure described above, other support staff members for the HRPP and IRB include an RIO Manager, a Reliance Analyst, and two IRB Analysts, and an IRB Specialist. The HRPP and IRB staff for HMH must comply with all ethical standards and practices. The duties and responsibilities for all staff are found in their respective job descriptions, and their performance is evaluated on an annual basis. The HMH HRPP staff reports to the Director of the Human Research Protection Program, who has day-to-day responsibilities for its operations.

1.10.5 Institutional Review Board (IRB)

HMH has one on site IRB, and also relies on external IRBs appointed by the Institutional Official (IO). The IRB prospectively reviews and makes decisions concerning all human research conducted at HMH facilities, by its employees or agents, or under its auspices unless another IRB has been designated to do so. The IRB is responsible for the protection of rights and welfare of human research subjects at the HMH, through review and oversight of safe and ethical research. It discharges this duty by complying with the requirements of federal and state regulations, the FWA, and organizational policies. (See Section 4 for a detailed discussion of the IRB.)

The IRB functions independently of, but in coordination with, other organizational committees and officials. The IRB, however, makes its independent determination whether to approve or disapprove a research plan based upon whether or not human subjects are adequately protected.

Research that has been reviewed and approved by the IRB may be subject to review and disapproval by officials of the organization. However, those officials may not approve human research that has not been approved or has been disapproved by the IRB.

HMH also uses the services of Western/Copernicus Institutional Review Board (WCG-IRB) and Advarra, and other external, Institutional IRBs for the review of most sponsored research, and NCI Cooperative Institutional Review Board (CIRB) serves as the IRB of record for cooperative research. As a cooperative partner with Georgetown, HMH cedes review of all cancer related research to the Georgetown IRB. HMH also has provisions for facilitating single review with any IRB who meets the requirements.

1.10.6 Counsel's Office

The HMH HRPP relies on the General Counsel for the interpretations and applications of state law and the laws of any other jurisdiction where research is conducted as they apply to human subjects research. General Counsel will also advise the IRB about other legal issues such as who is a child, and who can serve as a legally authorized representative or guardian. When there are any conflicts between federal or national law and other applicable laws, the General Counsel will determine the appropriate resolution.

1.10.7 Department Chairs and/or Organizational Leaders

Department Chairs and organizational leaders are responsible for ensuring that the investigator is qualified by training and experience to conduct the proposed research. For each research study submitted to HMH or designated IRB for approval, the department chair or leader must certify that s/he accepts responsibility for supporting adherence to the federal and state regulations and organizational policies governing the protection of human subjects of research, including applicable organizational credentialing requirements. Department chairs/leaders are responsible for assuring that investigators have the resources required to conduct the research in a way that will protect the right and welfare of participants. Such resources include but are not necessarily limited to personnel, space, equipment and time.

Department chairs/leaders are required to review all proposals before they are submitted to the IRB for review. The signature of the Department chair or leader indicates that (1) the investigator is qualified and has the necessary resources to safely conduct the study, and (2) attests to the scientific merit of this study, which means

- The research uses procedures consistent with sound research design;
- The research design is sound enough to reasonably expect the research to answer its proposed question;

1.10.8 The Investigator

The investigator is the ultimately responsible for the protection of the human subjects who participate in research. The investigator is expected to abide by the highest ethical standards when developing a research plan that incorporates the principles of the Belmont Report. The investigator is expected to conduct research in accordance with the IRB approved research plan and to oversee all aspects of the research by providing training and supervision of support staff, including oversight of the informed consent process. All subjects must give informed consent unless the requirement has specifically been waived by the IRB. Investigators must establish and maintain an open line of communication with research subjects within their responsibility. In addition to complying with all applicable policies and standards of regulatory bodies, investigators must comply with organizational and administrative requirements for conducting research. The investigator is responsible for ensuring that all research staff complete all organizational required training as well as training for their responsibilities in any given specific research study. When investigational drugs or devices are used, the investigator is responsible for providing a plan for their storage, security, dispensing, accounting, and disposal.

1.10.9 Other Related Units

1.10.9.1 Office of Research Administration

Under the Office of Research Administration, staff review all research agreements with all sponsors including federal, foundation, and non-profit sponsors. This review ensures that all terms of the award (grant or contract) are in compliance with organizational policies. Only designated individuals within Office of Research Administration have the authority to approve research proposals and to execute research agreements on behalf of the organization.

The Office of Research Administration ensures that required AAHRPP language (see Section 20.2) is included in contracts. The Office of Research Administration has access to all IRB submissions to confirm that the contract and the consent documents are consistent in terms of costs to subjects and who pays in case of injury. The Office of Research Administration and the IRB office coordinate efforts to ensure that all applicable individuals have filed appropriate COI disclosures to meet investigator COI policies.

When the grant or contract agreement includes human research activities that will be conducted by investigators who are not employees or agents of HMH, a subcontract is executed between HMH and the collaborating institution. The subcontract includes the requirement for the collaborating institution to assure compliance with federal regulations for the protection of human subjects in research and to provide documentation of current and ongoing IRB approval. The collaborating institution must also ensure that key personnel involved in human subject research are in compliance with the NIH policy on education in the protection of human research subjects and provide documentation of education of key personnel to HMH staff.

1.10.9.2 HMH Pharmacy

A pharmacist from HMHHMH serves on the IRB, allowing the Pharmacy to have complete information about all IRB approved research that takes place at HMH and under its jurisdiction. The Pharmacist member assures that information about all studies involving drugs used in research is shared with both the Pharmacy Staff as appropriate and that HMH Pharmacy is made aware of IRB approved research involving drugs.

The HMH hospital-based pharmacies or its affiliate pharmacies are responsible for storing, accounting for, dispensing, and compounding of most investigational drugs used in research, whether conducted inpatient or outpatients. The manufacture/compounding of drug products not commercially available is coordinated by the pharmacy. Waivers from use of the HMH pharmacies for handling investigational drugs will be considered on a case by case basis by both the IRB and the HMH Director of Pharmacy, with required information regarding storage, accounting, dispensing etc. provided within the IRB application.

The Research Pharmacists and Director is available to provide guidance to investigators in relation to the management of the study drugs.

1.10.10 Relationship Among Components

The Compliance Oversight Committee will meet to ensure a dialogue is maintained between the various compliance entities at the Organization. Membership is comprised of the VP and Chief Compliance Officer, Director of Research Operations, Pharmacy Director, and other relevant staff, with the Vice President for Research and Innovation as Chair. The committee will act in an advisory capacity to the Vice President for Research and Innovation, monitoring the effectiveness of existing compliance programs, developing new or revised policies as changes in requirements occur, and disseminating updated compliance information to the research community.

1.10.11 Study-Specific Coordination

In addition to IRB approval, the Investigator must obtain and document the approval, support, or permission of other individuals and departments or entities impacted by the research as well as approval by other oversight committees, including, but not limited to:

- Pathology
- University Hospital/Affiliated Hospital/s
- Pharmacy
- Radiology/Imaging
- Nursing
- Permission from external research locations (sites)
- Departmental approvals
- Database access permissions (e.g., Medical/Educational Records)
- Institutional Biosafety Committee
- Radiation Safety Committee

- Network Safety Committee
- Conflict of Interest Committee
- Scientific Review Committees
- Georgetown PMRS Committee for cancer research

For any that are indicated, a letter of support, collaboration, permission, or approval from the designated authority, should be included in the Initial Study Application to the IRB. The application will be reviewed in the IRB Office to ensure that all necessary letters are included. Final IRB approval will not be given until all necessary letters are received. The IRB may request review or consultation with any of the above listed or other organizational committees or components even when such review or consultation is not technically required by policy.

Other committees and officials may not approve research involving human subjects to commence that has not been approved or has been disapproved by the IRB.

1.11 Collaborative Research Projects

In the conduct of cooperative research projects, HMH acknowledges that each organization is responsible for safeguarding the rights and welfare of human subjects and for complying with applicable federal regulations. When a cooperative agreement exists, HMH may choose to 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 HMH and the other institution through an Institutional Agreement, a Memorandum of Understanding, or other such written agreement. This relationship must be formalized before HMH will accept any human research proposals from the other institution or rely on the review of the other institution.

It is the policy HMH to assure that all facilities participating in a study involving human subjects 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 investigator must identify all institutions participating in the research, the responsible IRB(s), and the procedures for dissemination of study information (IRB initial and continuing approvals, relevant reports of unanticipated problems, study modifications, and interim reports) between all participating institutions.

When the HMH IRB reviews research conducted in whole or in part at another institution, the particular characteristics of each institution's local research context must be considered, either (i) through knowledge of its local research context by the IRB or (ii) through subsequent review by appropriate designated institutional officials, such as the Chair and/or other IRB members.

If HMH is the coordinating facility the investigator must document how the conduct of the research plan and the protection of human subjects will be communicated to and among the other participating facilities engaged in the research study. The investigator is responsible for serving as the liaison with regulatory and funding 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 research plan 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.

The investigator must follow these procedures HMH is the coordinating facility:

- During the initial IRB submission of the multi-site study, the investigator indicates in writing on the application form or in an application letter that HMH is the coordinating facility of a multi-site study.
- The investigator submits the following information in the IRB application materials:
    - Whether research activities at participating institutions are defined as engagement
    - Name of each participating facility
    - Confirmation that each participating facility has an FWA (including FWA number and expiration date)
    - Contact name and information for investigator/s at each participating facility
    - Contact name and information for IRB of record at each participating facility
    - Method for assuring all participating facilities have the most current version of the research plan
    - Method for confirming that all modifications to the research plan are communicated to participating sites
    - Method for communicating to participating facilities any serious adverse events and unanticipated problems involving risks to subjects or others
    - Method of communicating regularly with participating sites about study events
- The investigator submits approval letters from all IRBs of record for all participating sites.
- The investigator maintains documentation of all correspondence between participating sites and their IRB of record.

When HMH is engaged in only part of a cooperative research project, the HMH IRB only needs to approve the part(s) of the research in which the HMH investigator is engaged. For example, if HMH is operating the statistical center for a multicenter trial that receives identifiable private information from multiple other institutions, the HMH IRB reviews and approves the research activities related to the receipt and processing of the identifiable private information by the statistical center.

2 Quality Assurance

HMH performs Quality Assurance and Improvement activities for the purposes of monitoring the safety of ongoing studies and measuring and improving human research protection effectiveness, quality, and compliance with organizational policies and procedures and applicable federal, state, and local laws.

2.1 External Monitoring, Audit, and Inspection Reports

All reports from external monitors, auditors, or inspectors must be submitted by investigators to the IRB for review. All routine monitoring reports may be submitted at the time of annual review. All audit or inspection reports must be submitted to the IRB upon receipt. The IRB Chair or designee will review such reports in order to monitor for issues that could impact the rights or welfare of human subjects and for issues indicative of possible serious or continuing non-compliance. If such issues are identified, the report will be forwarded to the convened IRB to determine what additional actions are necessary.

2.2 Investigator Compliance Reviews

The Corporate Compliance Office is responsible for conducting post-approval directed ("for cause") audits and periodic (not "for cause") compliance reviews of investigator research plans through the Clinical Research Auditing Plan. Additionally, the IRB or the Chief Compliance Officer may appoint a subcommittee for the purpose of conducting a for-cause or not for-cause compliance review of one or more research plans under its jurisdiction. The subcommittee may be composed of IRB members and staff from within, or individuals from and outside of the organization.

Compliance reviews are conducted to assess investigator compliance with federal, state, and local law, and HMH HRPP policies to identify areas for improvement, and to provide recommendations based on existing policies and procedures. The results of compliance reviews will be reported to the Chief Compliance Officer, the Director of the Human Research Protection Program, the IRB, and the investigator. Any non-compliance will be handled according to the procedures in Section 16.

If it is identified that subjects in a research project have been exposed to unexpected serious harm, the reviewer will promptly report such findings to the RIO Manager and the IRB Chair for immediate action.

If issues are identified that indicate possible misconduct in research, the procedures in the Research Misconduct Policy will be initiated.

Compliance reviews may include:

- Verify investigator qualifications

        - Review PI and sub-investigator CV's and registrations and verify documentation was current at time of study visit
        - Verify current certifications and lab normal ranges protocol-required procedures
        - Verify equipment not covered under CLIA or CAP certifications are adequately maintained and review certifications
- Verify facilities remain adequate throughout the trial
- Ensure drug dispensation and storage complies with regulatory requirements. Drug/Device accountability will include the review of (21 CFR 312.62 a, ICH 4.6.1)
    - Verify documentation in the master file of receipt of disposition/use and return of product.
    - Verify the master file contains guidelines for handling product
    - Verify the site maintains records that indicate product has been supplied only to eligible subjects at protocol specified doses
    - The investigator's records for study drug or study device shipping receipts including lot number and quantity (if applicable)
    - Shipping receipts to other sites (if applicable)
    - Review of dispensing logs including the subject initials, number, dose or quantity and person dispensing
    - Temperature log
    - Return receipts
    - Verify that the protocol or the master file documents how subjects are provided with necessary instruction on how to use, handle, store, and return product
- Verify the site is following the approved IRB protocol
- Ensure protocol deviations and violations are reported
- Verify Informed Consent process
    - Informed Consent review (21CFR 50)
    - Review of the signed informed consent documents for the correct version, completeness of the subject's or legally authorized representative signature and date, signature and date of person obtaining the consent, investigator signature and date, and witness name, signature and date when required.
    - Documentation of the informed consent process or enrollment note. The auditor should evaluate for documentation of the informed consent discussion including a question and answer period, the subject had adequate time to make an informed decision, signed the informed consent prior to the initiation of any study procedures and received a copy of the signed informed consent.
    - Verify correct version of IRB-approved consent form was used
    - Verify the subject completed a HIPAA form prior to enrollment
- Verify staff has adequate training and responsibilities have not been delegated to unauthorized individuals
- Report subject recruiting and enrollment rate

        - Compare the number of subjects who signed informed consent to the limit approved by the IRB
        - Check subject screening log to document subjects who entered screening but did not participate in the trial
    - Verify accuracy of records and completeness of CRF entries and ensure corrections are made when necessary. Review of the clinical record will include:
        - Verification of data using the medical records, research records, study logs and CRF is applicable
        - Documentation the subject meets inclusion criteria. (21 CFR312.312.62 b) (ICH 4.9.1, 4.9.2)
        - Documentation the subject did not meet exclusion criteria
        - Completion of protocol specific procedures and adherence to the study visit schedule
        - Verification that staff is performing study duties as detailed on the delegation of authority form and/or form 1572
        - Documentation of investigator or sub-investigator review of laboratory data, tests or protocol procedure results in a timely manner (i.e. prior to randomization or study visits)
    - Verify Adverse Events and serious adverse events are reported to the appropriate agencies
        - Ensure essential regulatory documents are maintained. Review of the site's Regulatory binder/file can include:

- PI and sub-investigator CV's and registrations
- FDA form 1572 and any revisions
- Sponsor financial disclosure forms. (21 CFR 54)
- FDA form 1571 and any revisions
- Essential laboratory documents including CAP, CLIA, reference ranges and the director's CV and registration (ICH 8.2.11, 8.2.12)
- Delegation of Authority form (ICH 4.1.5)
- Screening and enrollment logs
- IND safety or SAE reports (ICH 16.2)
- IRB or other review committee correspondence
- Copies of the protocol, amendments, informed consents, informed assents, HIPAA, advertising materials, investigator drug brochures, subject materials, and progress reports (ICH 8.2.2, ICH 8.2.1)
- DSMB reports or minutes
- Sponsor correspondence
- Annual progress reports to the appropriate regulatory agency
- Certificate of Confidentiality (if indicated)
- Documentation of protocol deviations or violations including IRB notification, sponsor notification or appropriate regulatory agency
- Final progress report if available
- Documentation of appropriate training

a) Conducting other monitoring or auditing activities as deemed appropriate by the HRPP or IRB.

2.3 IRB Compliance Reviews

The Research Compliance Auditors, with, or without, the assistance of an outside organization, will periodically review the activities of the IRB to assess compliance with regulatory requirements and to identify areas for improvement; this will include a review of IRB records at least annually. Review activities may include:

a) 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 risk/benefit ratio and consent issues that are included in the criteria for approval;
b) Review of the IRB minutes to assure that quorum was met and maintained;
c) Review of IRB documentation, including IRB minutes, to assess whether privacy provisions, according to HIPAA, have been adequately reviewed, discussed and documented;
d) Evaluating the continuing review discussions to assure they are substantive and meaningful and that no lapse has occurred since the previous IRB review;
e) Reviewing IRB files to assure retention of appropriate documentation and consistent organization of the IRB file according to current policies and procedures;
f) Reviewing the IRB database to assure all required fields are completed accurately;
b) Verifying IRB approvals for collaborating institutions or external performance sites;
c) Reviewing the appropriate metrics (for example, time from submission to first review) to evaluate the quality, efficiency, and effectiveness of the IRB review process;
d) Reviewing the workload of IRB staff to evaluate appropriate staffing level; and
e) Other monitoring or auditing activities deemed appropriate.

The Chief Compliance Officer, Director of the Human Research Protection Program, and the RIO Manager will review the results of IRB compliance reviews with the IRB and the Institutional Official. If any deficiencies are noted in the review, a corrective action plan will be developed by the RIO Manager and Director of the Human Research Protection Program and approved by the Institutional Official and the Chief Compliance Officer. The RIO Manager will have responsibility for implementing the corrective action plan, the results of which will be evaluated by the Corporate Compliance Office.

2.4 HRPP Quality Assessment and Improvement

A quarterly meeting is held by the Corporate Compliance Office and the Director of the Human Research Protection Program in which the quality improvement plan is put into place, to be

carried out by an individual or committee named by the Chief Compliance Officer that assesses compliance and achievement of targeted levels of quality, efficiency, and effectiveness of the HRPP (e.g., continuous investigator training; use of IRB-approved consent forms, turn-around time of exemption determinations, etc.). The plan will, at a minimum contain:

- Results of the metrics gathered during the year that reflect the results of the auditing and monitoring programs
    - An evaluation of the goals of the quality assessment/improvement plan with respect to measuring effectiveness, identifying opportunities for improvement and achieving and maintaining targeted levels of quality, efficiency, effectiveness
- At least one objective to achieve or maintain compliance is defined
- A review of the measures that are used to ensure industry standard benchmarks are being used and assessed
- At least one objective of quality, efficiency, or effectiveness is defined
- At least one measure of quality, efficiency, or effectiveness is defined
- A review of the methods to assess quality, efficiency, or effectiveness and make improvements are described, including a review of the Institutional Auditing Plans

The data is reviewed by the RIO Manager, Director of the Human Research Protection Program, VP of Research, QA Staff and the IO, in order to identify trends and to determine if systemic changes are required to prevent re-occurrence. If so, the RIO Manager and other relevant parties will collaborate in the development of a corrective action plan, its implementation, and evaluation of its effectiveness.

The IRB Specialists are responsible for tracking internal metrics that are informative in considering IRB and Investigator efficiency such as the amount of time from receipt of a submission through pre-review, assignment to the IRB, and final approval and the amount of time it takes investigators to develop and submit responses to pre-review and IRB requirements. Metrics reports can be run from the electronic system on an as needed basis.

Annually, the Director, in collaboration with other relevant parties, will define Quality Improvement goals for the year. The targeted issues, goals, and means to measure progress are documented in a written QA/QI plan. In order to evaluate whether the defined goals are being achieved, the Research Compliance Auditors collects, records, and provides a written report to the Director for tracking purposes. At the end of each year, the Directors evaluate whether the respective goals were achieved and adjusts the affected processes to correct any deficiencies.

3 Education & Training

3.1 Training / Ongoing Education of IRB Chair, Members, and Staff

Recognizing that a vital component of a comprehensive human research protection program is an education program. HMH is committed to providing training and an on-going educational process for IRB members and the staff of the IRB and HRPP Office, related to ethical concerns and regulatory and organizational requirements for the protection of human subjects.

Orientation

New IRB members, including alternate members will meet with a RIO staff member for an informal orientation session. At the session, the federal regulations will be reviewed and an orientation to IRB processes will be given. Also, the new member will be given an IRB Handbook (binder) that includes:

- Belmont Report;
- HMH Policies and Procedures for the Protection of Human Subjects;
- Federal regulations relevant to the IRB; and
- Tools used by IRB reviewers (checklists etc.).

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

Initial Education

IRB members and HRPP and IRB administrators and staff will complete the required modules in the CITI Course in the Protection of Human Research Subjects (biomedical or social behavioral track, as applicable), including the IRB Member Module - "What Every New IRB Member Needs to Know" and the module on Conflicts of Interest. Community members are expected to review the "I Have Agreed to be an IRB Community Member. Now What?" module as well.

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.

In addition to initial training requirements, IRB members and HRPP and IRB administrators and staff must also satisfy continuing education requirements on an annual basis HMH uses the following activities as a means for offering continuing education to IRB members and HRPP and IRB administrators and staff:

- In-service training at IRB meetings;
- Annual IRB training seminar
- Training workshops;

- Copies of appropriate publications;
- Identification and dissemination by the Director of new information that might affect 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; and
- Unlimited access to the IRB Office resource library.

IRB members and HRPP and IRB administrators and staff are also required to complete CITI training every 3 years as part of the HMH continuing education requirements.

The activities for continuing education vary on a yearly basis depending on operating budget and areas of need, as determined by the Director of the Human Research Protection Program. The Director of the Human Research Protection Program determines which continuing education activities are mandatory for IRB members and staff in a given year. The RIO Manager tracks whether each individual has satisfied the requirements. Continuing failure to complete training may result in the individual being removed or not renewed as an IRB member. Fulfillment of training requirements is included as part of the evaluation of the performance of IRB members/alternates.

Members and staff who are unable to attend education sessions will be provided with the opportunity to make-up any training that they missed. If a make-up session is not possible (e.g., a webinar or conference), then an equivalent educational opportunity will be offered at the discretion of the Director.

The Institutional Official (IO) will provide support to send as many members of the IRB as possible to attend the annual PRIM&R conference or regional OHRP conferences on human research protections.

3.2 Training / Ongoing Education of Investigators and Research Team

As stated previously, a vital component of a comprehensive human research protection program is an education program for all individuals involved with research subjects. HMH 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 organizational requirements for the protection of human subjects.

3.2.1 Initial Education

CITI Program Modules

Investigators, key personnel, and other members of the research team must complete HMH required core modules in the CITI Course in the Protection of Human Research Subjects including the module on Conflicts of Interest. Evidence of current training (date of completion within 3 years of application date) for each member of the research team must be included in every new research study application and application for continuing review. New research

plans and applications for continuing review will not be approved from investigators who have not completed the initial education requirement.

While research plans and applications for continuing review will be accepted and reviewed if the investigator holds a current certification of training, final approval will not be granted until all sub-investigators and members of the research team have completed the initial education requirement.

Clinical Research Education Program

All research staff will be required to attend the appropriate training designated by the Clinical Research Education Program. Staff hired into research roles will be required to attend the Clinical Research training program. This program consists of 4 half day training sessions.

Waiver of Initial Education

If individuals can provide documentation verifying that they have successfully completed the CITI Program at another institution, they may affiliate themselves with HMH via the CITI Program site. Additional modules may need to be completed if previously completed modules do not meet our minimum coursework requirements. All investigators or members of their research team must complete the requirements of Continuing Education as reviewed below.

3.2.2 Continuing Education and Recertification

Investigators, key personnel, and other members of the research team must meet the HMH continuing education requirement every three (3) years after certification of Initial Education for as long as they are involved in human subject research. There is no exception to this requirement.

In addition to the required CITI Program training, research staff is expected to attend at least six training sessions offered during the year by the Office of Research Administration.

Additional acceptable training includes attendance at approved PRIM&R, OHRP, or FDA seminars and conferences, attendance at 6 number of HRPP Human Subject Research Presentations, or review of appropriate refresher modules at the CITI web-based training site. Other training may be acceptable. In these cases the investigator should check with the Research Integrity Office for a determination.

Individuals must submit to the IRB office evidence of continuing education prior to the expiration of their training certification. New research plans and applications for continuing review will not be accepted from investigators who have not submitted satisfactory evidence of continuing education.

Investigators who are also IRB Chair, IRB members, or IRB Office staff will satisfy the training requirements for IRB members and staff described in this policy under Section 3.1.

4 Institutional Review Board

HMH has established an Institutional Review Board (IRB) to ensure the protection of human subjects in research conducted under the auspices of the HMH. All non-exempt human subject research conducted under the auspices of the HMH must be reviewed and approved by the HMH IRB or another designated IRB prior to the initiation of the research.

Although HMH has authorized a number of IRBs to fulfill the review and oversight function, all on-site IRBs follow the same policies and procedures. Therefore, for the purposes of this document, all on-site IRBs will be referred to as the Hackensack Meridian Health IRB (HMH IRB).

HMH also uses the services of off-site IRBs. These include, but are not limited to:

- Western Institutional Review Board
- Advarra Institutional Review Board
- NCI's Adult CIRB: for applicable cooperative oncology group protocols/studies involving adult subjects
- NCI's Pediatric CIRB: for applicable cooperative oncology group protocols/studies involving minor subjects

The authorized off-site IRBs that serve as the IRB-of-record for HMH have the same authority as the on-site IRBs and all determinations and findings of the off-site IRBs are equally binding on all research under the auspices of the organization.

4.1 IRB Authority

The IRB derives its authority from HMH HRPP policy, as cited in Section 1.2 above. Under the federal regulations, IRBs have the authority:

1. To approve, require modifications to secure approval, or disapprove all human subjects research activities overseen and conducted under the auspices of HMH;
2. To require that informed consent be obtained and documented in accordance with regulatory requirements unless the criteria for the waiver or alteration of such requirements has been satisfied and approved by the IRB. The IRB may require that information, in addition to that specifically mentioned in the regulations, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects;
3. To conduct continuing review of research at intervals appropriate to the degree of risk of the research, but not less than once per year;
4. 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;
5. To observe, or have a third party observe, the consent process; and

6. To observe, or have a third party observe, the conduct of the research.

The IRB functions independently. Attempts to coerce or otherwise unduly influence the actions of the IRB are forbidden by policy, and are to be reported as described in Section 4.7. Likewise, the IRB must remain free from the influence of financial and other organizational interests. No individual with responsibility for the business and financial interests of the organization may serve on the IRB. In addition, no IRB member or alternate may participate in the review of any research project in which the member has a conflict of interest (COI), except to provide information as requested (See Section 21.1.2).

Research that has been reviewed and approved by the IRB may be subject to review and disapproval by officials of the organization. However, those officials may NOT approve research if it has not been approved or has been disapproved by the IRB. Reviewing officials may strengthen requirements and/or conditions, or add other modifications before approval or may require approval by an additional ancillary committee. Previously approved research proposals and/or consent forms must be re-approved by the IRB before initiating any changes or modifications that result from such additional reviews/approvals.

4.2 Roles and Responsibilities

4.2.1 Chair of the IRB

The Institutional Official appoints the Chair and Vice Chair in renewable terms with the approval of the CEO. Any change in appointment, including reappointment or removal, requires written notification.

The IRB Chair should be a highly respected individual, from within the HMH, fully capable of managing the IRB, and the matters brought before it with fairness and impartiality. The task of making the IRB a respected part of the research community falls primarily on the shoulders of the Chair. The IRB must be perceived to be fair, impartial and immune to pressure by administration, the investigators whose research plans are brought before it, and other committees and professional and nonprofessional offices/sources.

The IRB Chair is responsible for conducting the meetings, conducting expedited reviews and may serve as signatory for correspondence generated by the IRB.

The IRB Chair is authorized to take immediate action to suspend a study or studies if information is presented regarding subject safety or for any other reason where such action would be deemed appropriate. Such action requires subsequent notice to and review by the convened IRB.

The IRB Chair may designate other experienced IRB members to perform duties such as expedited reviews and other IRB functions.

The IRB Chair advises the Institutional Official, the Director of the HRPP, and the RIO Manager about IRB member performance and competence.

The performance of IRB Chair will be reviewed on an annual basis by the Manager, Research Integrity Office and the Director of the HRPP in consultation with the Institutional Official.

Feedback from this evaluation will be provided to the Chair. If the Chair is not acting in accordance with the IRB's mission, or following these policies and procedures, has an undue number of absences, or not fulfilling the responsibilities of the Chair, he/she may be removed.

4.2.2 Vice Chair of the IRB (if applicable)

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

The performance of IRB Vice Chair will be reviewed on an annual basis by the Manager, Research Integrity Office in consultation with the Institutional Official. Feedback from this evaluation will be provided to the Chair. If the Chair is not acting in accordance with the IRB's mission, or following these policies and procedures, has an undue number of absences, or not fulfilling the responsibilities of the Chair, he/she may be removed.

4.2.3 IRB Members

The role of an IRB member is to ensure that human research activities comply with federal regulations, state and local laws, and organizational policies and procedures, by:

1. Completing member education and training, both initial and on-going (See Section 3.1).
2. Maintaining the confidentiality of IRB deliberations and research review by the IRB.
3. Conducting and documenting reviews of assigned research in a timely fashion.
4. Attending IRB meetings as scheduled.
   Members should attend all meetings for which they are scheduled. If a member is unable to attend a scheduled meeting, they should inform the RIO Supervisor or Manager.

   If an IRB member is to be absent for an extended period of time, he or she must notify the RIO Manager in advance so that an appropriate alternate/replacement can be obtained. If the member has a designated alternate, the alternate can serve during the primary member's absence.
5. Recusing self from final deliberations and vote when s/he has a conflict of interest
6. Participating in subcommittees of the IRB if requested and available.
7. Conduct themselves in a professional and collegial manner.

The performance of IRB members will be reviewed on an annual basis by the RIO Supervisor and Manager in consultation with the Director. IRB members will receive formal documented feedback on the results of this review. Members who are not acting in accordance with the IRB's mission or not following policies and procedures or who have an undue number of absences may be removed.

4.2.4 Alternate members

The appointment and function of alternate members is the same as that for primary IRB members. An alternate's expertise and perspective should be comparable to those of the

primary member. The role of the alternate member is to serve as a voting member of the IRB when the regular member is unavailable to attend a convened meeting. When an alternate member substitutes for a primary member, the alternate member will receive and review the same materials prior to the IRB meeting that the primary member received or would have received.

The IRB roster identifies the primary member(s) or class of members (e.g., physician scientist) for whom each alternate member may substitute. The alternate member will not be counted toward meeting quorum as a voting member unless the primary member is absent. The IRB minutes will document when an alternate member replaces a primary member.

Experienced alternate members may be designated by the Chair to conduct expedited reviews.

4.2.5 Subcommittees of the IRB

The IRB Chair, in consultation with the RIO Manager, may designate one or more other IRB members to a subcommittee of the IRB to perform duties, as appropriate, and undertake other IRB functions, and to make recommendations to the IRB (e.g., to supplement the IRB's initial review, continuing review, review of modifications, and/or review of reports of unanticipated problems or of serious or continuing non-compliance). The IRB Chair, in consultation with the RIO Manager, will appoint IRB members to serve on each IRB Subcommittee created under this Section. The number and composition of the IRB Subcommittee members shall depend on the scope of duties delegated by the IRB Chair to such IRB Subcommittee (e.g., making recommendations, conducting an inquiry, etc.). Any such Subcommittee cannot approve research that requires approval at a convened IRB meeting.

4.3 IRB Membership

The structure and composition of the HMH IRB is 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 the HMH.

The IRB will include members who are knowledgeable about and experienced working with vulnerable populations that typically participate in HMH 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. HMH has procedures (See Section 7.4.1.1) that specifically outline the requirements of research plan review by individuals with appropriate scientific or scholarly expertise. A member of the IRB may fill multiple membership position requirements for the IRB.

Individuals from HMH Office of Research Administration, Office of Development or Office of Technology Transfer may not serve as members of the IRB or carry out day-to-day operations of the review process. Individuals from these offices may provide information to the IRB and attend IRB meetings as invited guests.

4.4 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 organization.
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 organizational commitments 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.
5. Every nondiscriminatory effort will be made to ensure that the IRB does not consist entirely of men or entirely of women, including the organization's consideration of qualified persons of both sexes, so long as no selection is made to the IRB solely on the basis of gender. The IRB shall not consist entirely of members of one profession.
6. The IRB includes at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.
7. The IRB includes at least one member who is not otherwise affiliated with the organization and who is not part of the immediate family of a person who is affiliated with the organization.
8. The IRB includes at least one member who represents the general perspective of participants.
9. One member may satisfy more than one membership category.
10. The IRB Chair and Vice-Chair are voting members of the IRB.
11. The Manager and staff of HMH IRB Office may be voting members of the IRB.

On an annual basis, the IRB Chairs and the RIO Manager shall review the membership and composition of the IRB to determine if they continue to meet regulatory and organizational requirements. Members will receive documented feedback on their performance as reviewers following this annual review.

4.4.1 Appointment of Members to the IRB

When the IRB Chair, HRPP Director and RIO Manager of the IRB Office identifies a need for a new, replacement, or alternate member, the names of candidates will be sent to the RIO Office. Department Chairs may forward nominations to the Institutional Official, or to the RIO Office for consideration.

Initial appointments are made for a one-year term. Subsequent appointments are made for a renewable three-year period of service. Any change in appointment, including reappointment or removal before the end of a member's term, requires written notification. Members may resign by written notification to the Chair, Manager or Director.

On an annual basis, the IRB Chair and the RIO Manager reviews the membership and composition of the IRB to determine if they continue to meet regulatory and institutional requirements.

4.4.2 IRB Registration Updates

Changes in IRB membership will be reported to FDA and OHRP as follows:

1. An HMH decision to disband a registered IRB that it is operating will be reported in writing within 30 days after permanent cessation of the IRB's review of DHHS-conducted or supported research.
2. If an FDA-regulated IRB decides to review additional types of FDA-regulated products (e.g., to review device studies if it only reviewed drug studies previously) or to discontinue reviewing clinical investigations regulated by FDA, it must report this within 30 days of the change.
3. Within 90 days after changes regarding the contact person who provided the IRB registration information or the IRB Chair.
4. To register any additional IRB before it is designated under an FWA and reviews research conducted or supported by DHHS or regulated by FDA.
5. Within 90 days of a change in the membership roster if that IRB is designated under an FWA.

4.5 Use of Consultants

When necessary, the IRB Chair, Director, HRPP or the RIO Manager may solicit individuals from the organization or the research community with competence in special areas to assist in the review of issues or research plans, which require appropriate scientific or scholarly expertise beyond or in addition to that available on the IRB. The IRB Office will ensure that all relevant materials are provided to the outside reviewer prior to the convened meeting.

Written statements from consultants will be kept in the IRB records. Key information provided by consultants at meetings will be documented in the minutes. Written reviews provided by the outside reviewer will be filed with the study records.

The RIO Manager reviews the conflicting interest policy for IRB members with consultants and consultants must confirm that they do not have a conflict of interest prior to review. Individuals who have a conflicting interest or whose spouse or immediate family members have a conflicting interest in the sponsor of the research will not be invited to provide consultation.

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

Ad hoc or informal consultations requested by individual members (rather than the convened board) will be processed by the IRB Office in a manner that protects the investigator's confidentiality and is in compliance with the IRB conflict of interest policy.

4.6 Liability Coverage for IRB Members

The HMH insurance coverage applies to employees and any other person authorized to act on behalf of HMH for acts or omissions within the scope of their employment or authorized activity.

4.7 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 Chief Compliance Officer or Institutional Official (IO), depending on the circumstances. The IO will ensure that a thorough investigation is conducted and if the allegation is determined valid, that corrective action is taken to prevent additional occurrences. In the event that the allegation is regarding the IO, the matter will be referred to Chief Compliance Officer for investigation and any necessary action.

Undue influence means attempting to interfere with a normal functioning and decision making of the IRB or to influence an IRB member of staff, or any other member of the research team outside of the establish processes or normal and accepted methods in order to obtain a particular result, decision or action by the IRB or one of its members or staff.

5 Human Subject Research Determinations

The responsibility for initial determination whether an activity constitutes human subject research rests with the investigator. The investigator should make this determination based on the definitions of "human subject" and "research" in Section 1.3. Because they will be held responsible if the determination is not correct, investigators are urged to request a confirmation that an activity does not constitute human subject research from the Research Integrity Office. When research involves the use of coded private information or specimens, and the investigator makes an initial determination that the research does not include "human subjects", the investigator must request confirmation following the procedures described below. All requests include sufficient description of the activity and the rationale for the investigator's initial determination as outlined in the electronic form.

Examples of activities that are not considered research under the above definitions:

- **Quality Assurance/Improvement:** Activities whose purposes are limited to: (a) implementing a practice to improve the quality of patient care, and (b) collecting patient or provider data regarding the implementation of the practice for clinical, practical, or administrative purposes. Planning to publish an account of a quality improvement project does not necessarily mean that the project fits the definition of research
- **Case Reports:** The external reporting (e.g., publication, poster or oral presentation) of an interesting clinical situation or medical condition of up to three patients. The patient information used in the report must have been originally collected solely for non-research purposes as the result of a clinical experience.
- **Public Health Surveillance:** A series of ongoing systematic activities, including collection, analysis, and interpretation of health-related data essential to planning, implementing, and evaluating public health practice closely integrated to the dissemination of data to those who need to know and linked to prevention and control.

Determinations whether an activity constitutes human subject research will be made according to the definitions in Section 1.3 using the **Non-Human Subjects Research Determination** form. Determinations regarding activities that are either clearly human subject research or clearly not human subject research, based on the checklist answers, may be made by the RIO staff. Determinations regarding less clear-cut activities will be referred to the IRB Chair, who may make the determination or refer the matter to the full IRB.

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

6 Exempt Determinations

All research using human subjects must be approved by the HMH IRB. However, certain categories of human subject research are exempt from IRB approval. Exempt research is subject to review for determination of exemption status. At HMH, exemptions are reviewed and granted by the RIO Manager or experienced RIO staff.

Individuals involved in making the determination of an IRB exempt status of a proposed research project cannot be involved in the proposed research. Reviewers must not have any apparent conflict of interest. Identification of individuals designated to conduct exempt determinations will be made in writing.

Exemptions are determined or granted, rather than approved. Exempt studies are exempt from the Common Rule [45 CFR 46] (i.e., FWA, IRB approval and full research consent are not required). They do require a determination/confirmation of exemption status. Although exempt research is not covered by the federal regulations, this research is not exempt from ethical considerations, such as honoring the principles described in the Belmont Report. The individual/s making the determination of exemption will determine whether to require additional protections for subjects in keeping with ethical principles (e.g., requiring disclosure/consent, etc.).

6.1 Limitations on Exemptions

Children: The exemption for research involving survey or interview procedures or observations of public behavior (#2) does NOT apply to research in children, except for research involving observations of public behavior when the investigator does not participate in the activities being observed.

Prisoners: Exemptions do NOT apply. IRB review is required**.**

6.2 Categories of Exempt Research

1. Research, conducted in established or commonly accepted educational settings that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:

i. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
ii. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
iii. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by .111(a)(7): *When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data*.

3. (i) Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:

    A. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
    B. Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
    C. The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by .111(a)(7): *When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data*.

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

subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

4. Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:
    i. The identifiable private information or identifiable biospecimens are publicly available;
    ii. Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;
    iii. The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or
    iv. The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for non-research activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.

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

in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

6. Taste and food quality evaluation and consumer acceptance studies:

   i. If wholesome foods without additives are consumed, or
   ii. If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

6.3 FDA Exemptions

The following categories of clinical investigations are exempt from the requirements for prior IRB review and approval:

1. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article is subject to IRB review. [21 CFR 56.104(c)]

   Note: See Section 13.2 for detailed discussion of this exemption.

2. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the FDA 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)]

6.4 Procedures for Exemption Determination

In order to obtain an exemption determination, investigators must submit:

1. Completed **Exempt Determination electronic form**;
2. All recruitment materials (e.g., letter of invitation, recruitment script, flyer);
3. Consent form/disclosure/information sheet (when appropriate);
4. All surveys, questionnaires, instruments, etc.;
5. Letter(s) of permission from each non-HMH site of performance;
6. If sponsored/funded, one copy of the grant application(s) and/or contract; and
7. Verification of current human research protection training for all members of the research team, including the faculty advisor.

The RIO Manager in consultation with the IRB Chair reviews all requests for exemptions and determines whether the request meets the criteria for exempt research.

To document the reviewer's determination of the request for exempt research, the reviewer completes the **Exemption Determination Checklist**. The reviewer verifies on the form whether the submission meets the definition of human subject research (See Section 5). If the request meets the definition of human subject research, the reviewer then determines whether or not the research is eligible for exemption. Although exempt research is not covered by the federal regulations, this research is not exempt from the ethical guidelines of the Belmont Report.

The individual making the determination of exemption will determine whether to require additional protections for subjects in keeping with the guidelines of the Belmont Report.

If there are interactions with participants, the reviewer should determine whether there should be a consent process that will disclose such information as:

- That the activity involves research.
- A description of the procedures.
- That participation is voluntary.
- Name and contact information for the researcher

The reviewer indicates whether the request for exemption was approved or denied, and if approved, the rationale for the determination and category/s under which it was permitted. The exempt application, review form, and determination letter are recorded and maintained in the same manner and for the same length of time as other IRB review documentation.

Once exemption review is completed, IRB staff will send written notification of the results of the review to the investigator.

Exempt determinations will include a termination date, with the maximum time allotted being 3years. If the investigator wants the research to extend beyond the termination date, the investigator must request another exemption determination. This process will allow the investigator and the organization the opportunity to review and update the research activity and determine whether or not it still qualifies for exemption. Similarly, investigators should report to any proposed modifications to the research during the course of the exempt study for a determination of whether or not the modified activity still qualifies for exemption. Finally, investigators must notify the IRB office when an exempt research project is complete so that the organization can maintain an accurate database of active research.

After a determination is made, the reviewer will file the study in the archives. Investigators must report any proposed modification to the research during the course of the exempt study for a determination of whether or not the modified activity still qualifies for exemption. Investigators must notify the IRB office when an exempt research project is complete so that the organization can maintain an accurate database of active research.

When the research requires limited IRB review or a HIPAA determination (i.e., waivers or alterations of the requirement for HIPAA authorization), the review may be conducted using

expedited review procedures by the IRB Chair or an experienced Chair-designated member of the IRB. As with all other research subject to IRB review requirements, when conducting limited IRB review the IRB has the authority to approve, require modifications in (to secure approval), or disapprove all research activities; and to suspend or terminate IRB approval. Actions of disapproval may only be made by the convened IRB. [45 CFR 46.109(a), 45 CFR 46.110]
Proposed modifications to the aspects of research subject to limited IRB review must be submitted to and approved by the IRB prior to implementation, except when necessary to eliminate apparent immediate hazards to the subject(s), in which case the change must be promptly reported to the IRB (i.e., within 5 business days). [45 CFR 46.108(a)(3)(iii)]
Continuing review is generally not required for research determined to be exempt, even when that research is subject to limited IRB review. However, the IRB may determine that continuing review is required for a particular study subject to limited IRB review, in which case it shall document the reasons for its determination in the IRB record and communicate the requirement to the investigator in the IRB determination letter. [45 CFR 46.109(f)(ii), 45 CFR 46.115(a)(3)]

7 IRB Review Process

The IRB will review and ensure that HMH research involving human subjects meets all required ethical and regulatory criteria for initial and continuing review and any modifications of approved research. The IRB may conduct their review using the following review methods:

- Expedited Review
- Review by Convened IRB

The following describe the procedures required for the review of research by the on-site IRB. (See section 9 for a description of the procedures for review of research by the off-site IRBs.)

7.1 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 acceptability of the risk-to-benefit analysis or increases the level of risks to subjects
2. The research design or methods (adding procedures that are not eligible for expedited review (See Section 7.2.2) would be considered more than a minor change)
3. The number of subjects enrolled in the research (usually not greater than 10% of the total requested locally)
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 majority (more than half) of the voting membership, including at least one member whose primary concern is in a non-scientific area. When research involving an investigational new drug is on the agenda for review, a physician should be included in the quorum.

Suspension of IRB approval. A suspension of IRB approval is a directive of the IRB to temporarily stop some or all previously approved research activities. Suspended research studies remain open and require continuing review.

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

7.2 Expedited Review

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

1. Some or all of the research appearing on the list of categories of research eligible for expedited review and found by the reviewer(s) to involve no more than minimal risk.
2. Minor changes in previously approved research during the period (of one year or less) for which approval is authorized. Note: review of minor changes does not alter the end-date of study approval.

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

7.2.1 Categories of Research Eligible for Expedited Review

The HMH IRB applies the categories of research eligible for expedited review, which were published in the Federal Register notice 63 FR 60364-60367, November 9, 1998.

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

The categories in this list apply regardless of the age of subjects, except as noted in category 2.

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.

When a reviewer determines that research subject to the Common Rule falls within the expedited categories but involves more than minimal risk, the reviewer will document the rationale for that determination in the checklist and refer the research for review by the convened IRB. If the research otherwise does not meet the criteria for expedited review, then the reviewer will indicate that the research requires review by the convened IRB and the submission is placed on the next available IRB meeting agenda.

Research Categories one (1) through seven (7) may be used for both initial and continuing IRB review:

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

(a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(a) from healthy, 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. (Note: Children are defined as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.)

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

Examples: (a) hair and nail clippings in a non-disfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) un-cannulated 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 sub-gingival 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; (k) vaginal swabs that do not go beyond the cervical os; rectal swabs that do not go beyond the rectum; and nasal swabs that do not go beyond the nares.

(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. (Note: 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 non-research 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)(2) and b(3). 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.)

Categories 8 and 9 apply only to continuing review.

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

(a) Where (i) the research at HMH 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 (Note: "Long-term follow-up" includes research *interactions* that involve no more than minimal risk to subjects (e.g.,

quality of life surveys); and collection *of follow-up* data from procedures or interventions that would have been done as part of routine clinical practice to monitor a subject for disease progression or recurrence, regardless of whether the procedures or interventions are described in the research study, but not *interventions* that would not have been performed for clinical purposes, even if the research interventions involve no more than minimal risk.); ***or***

(b) Where no subjects have ever been enrolled at HMH and no additional risks have been identified (Note: "no additional risks have been identified" means that neither the investigator nor the IRB has identified any additional risks from any institution engaged in the research project or from any other relevant source since the IRB's most recent prior review.); ***or***

(c) Where the remaining research activities at HMH are limited to data analysis. (Note: Simply maintaining individually identifiable private information without using, studying, or analyzing such information is not human subject research and thus does not require continuing review.

(9) Continuing review of research previously approved by the IRB at a convened meeting that meets the following conditions:

- The research is not conducted under an investigational new drug application (IND) or an investigational device exemption (IDE);
- Expedited review categories (2) through (8) do not apply to the research;
- The IRB has determined and documented at a convened meeting that the research, or the remaining research activity involving human subjects, involves no greater than minimal risk to the subjects; and
- No additional risks of the research have been identified. (Note: "no additional risks have been identified" means that neither the investigator nor the IRB has identified any additional risks from any institution engaged in the research project or from any other relevant source since the IRB's most recent prior review.)

7.2.2 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.

On an annual basis, the Chair will designate a list of IRB members eligible to conduct expedited review. The designees must be experienced (having served on the IRB for at least one year) voting members or alternate members of the IRB. The IRB Staff will select expedited reviewers from that list. Selected reviewers will have the qualifications, experience and knowledge in types of research 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 21.2) will not be selected.

When reviewing research under an expedited review procedure, the IRB Chair, or designated IRB member(s), will receive and review all documentation that would normally be submitted for a full-board review. This requirement applies to all categories of submissions including initial reviews, continuing reviews, and modifications. The reviewer will determine and document the regulatory criteria allowing use of the expedited review procedure by using the **Expedited Review Determination Form**.

If the research meets the criteria allowing review using the expedited procedure, the reviewer(s) conducting initial or continuing review will complete the appropriate review form checklist (**Initial Study Review Form** or **Continuing Review Form**) to determine whether the research meets the regulatory criteria for approval. The same criteria of approval apply to reviews conducted via expedited review as to those conducted by the convened board. 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 research study will be placed on the next available agenda for an IRB meeting.

In reviewing the research, the reviewers will follow the Review Procedures described in Sections 7.2 and 7.4 and may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure by the convened IRB (see Section 7.3).

Reviewers will indicate approval, required modifications or requirement for convened board review on the Study Review Form and return it to the IRB Office. If modifications are required, the IRB Office staff will inform the investigator in writing.

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 or the study will be referred to the convened IRB for review.

7.2.3 Informing the IRB

All members of the IRB will be apprised of all expedited review approvals by means of a list in the agenda for the next scheduled meeting. Any IRB member can request to review any study by contacting the IRB Office.

7.3 Convened IRB Meetings

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

7.3.1 IRB Meeting Schedule

The IRB meets on a regular basis throughout the year (usually twice per month). The schedule for the IRB may vary due to holidays or lack of quorum. The schedule for IRB meetings is

posted on the research web pages. Special meetings may be called at any time by the Chair or RIO Manager.

7.3.2 Preliminary Review

The RIO Manager or a staff member designated by the Manager will perform a preliminary review of all submissions for determination of completeness and accuracy, including an informed consent checklist, when applicable. 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 the agenda. If an investigator is submitting for the first time or is not well-versed in the submission procedures, consultations can be arranged with IRB staff.

7.3.3 Primary and Secondary Reviewers

After it has been determined that the submission is complete, the RIO Manager, with the assistance of the IRB Chair as needed, will assign submissions for review paying close attention to the subject matter of the research, the potential reviewer's area/s of expertise and representation for any vulnerable populations involved in the research. One "primary reviewer" will be assigned to each submission to receive and review the full submission materials. A reviewer may be assigned several submissions or other items for review. When the IRB is presented with a research study which may be outside of the knowledge base or representative capacity of the IRB members, an outside consultant will be sought (See Section 4.5). Research studies for which appropriate expertise cannot be obtained for a given meeting will be deferred to another meeting when appropriate expertise is available.

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. Beginning the discussion of the proposed research at the convened meeting, by summarizing the proposed research and leading the IRB through the regulatory criteria for approval (See Section 7.4).
4. Making suggestions for changes to the proposed research, where applicable.
5. Completing all applicable IRB reviewer forms.

One or more "secondary" reviewers may be assigned in addition to the primary reviewer. A secondary reviewer may be assigned to review the full submission materials or may be asked to review specified sections of the submission (e.g., the consent/assent/permission forms).

All IRB members receive and are expected to review all studies, not just those assigned as primary [or secondary] reviewer.

When it can be anticipated that the primary reviewer may be absent from the meeting, a new primary reviewer may be assigned, providing that they have sufficient time to review the materials in advance of the meeting. Additionally, an absent reviewer can submit their written

comments for presentation at the convened meeting. If an absent reviewer submits comments, those can indicate a recommendation regarding approval, but such recommendation will not be counted as a vote.

7.3.4 Materials received by the IRB

All required materials need to be submitted to the IRB office 14 days prior to the convened meeting for inclusion on the IRB agenda. The meeting agenda will be prepared by the IRB coordinator in consultation as needed with the RIO Manager or IRB Chair. All IRB members receive the IRB agenda, prior meeting minutes, applicable business items, continuing education materials and research submission materials no later than 5 business days before the scheduled meeting to allow sufficient time for the review process.

Each IRB member receives and reviews the following documentation, as applicable, for all studies on the agenda:

- A Protocol/Research Plan Summary or the complete Protocol
- The Study Application
- Proposed Consent / Parental Permission / Assent Form(s)
- Recruitment materials including advertisements intended to be seen or heard by potential subjects

The primary reviewers receive and review, in addition to the above, (1) the full protocol/research plan, (2) any relevant grant applications; and, (3) the investigator's brochure (when one exists) and/or other risk information. Additionally, for DHHS-supported multicenter clinical trials, the primary reviewer should receive and review a copy of the DHHS-approved sample informed consent document(s) (when one exists) and the complete DHHS-approved protocol/research plan (when one exists).

The materials provided to the primary reviewer are available to all members. Any IRB member may request any of the materials provided to the reviewers by contacting the IRB Office.

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

7.3.5 Quorum

A quorum of the IRB consists of a majority (more than half) of the voting membership, including at least one member whose primary concern is in a non-scientific area. When research involving an investigational new drug is on the agenda for review, a physician should be included in the quorum. At meetings of the IRB, a quorum must be established and maintained for the deliberation and vote on all matters requiring a vote.

The IRB Chair, with the assistance of the IRB staff, will confirm that quorum is present before calling the meeting to order. The IRB Chair, with the assistance of the IRB staff, will be responsible to ensure that the IRB meeting remains appropriately convened. If a quorum is not maintained, either by losing a majority of the members, losing all non-scientific members or

another required member, the IRB cannot take further actions or vote on regulatory determinations until quorum is restored.

It is generally expected that at least one unaffiliated member and at least one member who represents the general perspective of participants (one individual can serve in both capacities) will be present at all IRB meetings. The IRB may, on occasion, meet without this representation; however, this should be the exception.

If the IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or persons with impaired decision-making capacity, one or more individuals (e.g., IRB members, alternate members, or consultants) who are knowledgeable about and experienced with those subjects should be present during the review of the research.

IRB members are considered present and participating at a duly convened IRB meeting when either physically present or participating through electronic means (e.g., teleconferencing or video conferencing) that permits them to listen to and speak during IRB deliberations and voting. Whether or not physically present, the IRB member must have received all pertinent materials 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.

7.3.6 Meeting Procedures

The IRB Chair will call the meeting to order, once it has been determined that a quorum is in place. The Chair will remind IRB members to recuse themselves from the discussion and votes by leaving the room when they have a conflict. The IRB will review and discuss the 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 major revisions/corrections are necessary, the minutes will be amended and presented at the following IRB meeting.

The IRB reviews all submissions for initial and continuing review, as well as requests for modifications. The Reviewer presents an overview of the research and can assist the Chair in leading the IRB through the completion of the regulatory criteria for approval in the Institutional Review Board Study Review checklist. In order for the research to be approved, it must receive the approval of a majority of those voting members present at the meeting.

7.3.7 Guests

Investigators and research staff may be invited to the IRB meeting, at the discretion of the IRB, to make a brief presentation or to answer questions about proposed or ongoing research. The investigator/research staff may not be present for the deliberations or vote on the research.

The Director of the Human Research Protection Program and staff regularly attend IRB meetings and may participate in the IRB discussion and deliberations, but may not vote.

Other guests may be permitted to attend IRB meetings at the discretion of the IRB Chair and the RIO Manager. Such guests may be asked to sign a confidentiality agreement and do not participate in discussion unless requested by the IRB, under no circumstances may they vote.

7.4 Criteria for IRB Approval of Research

In order for the IRB to approve human subjects research, either through expedited review or by the convened IRB, it must be determined that the following requirements are satisfied. These criteria apply to all categories of IRB reviews including initial reviews, continuing reviews, and modifications of previously approved research.

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

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disable persons, or economically or educationally disadvantaged persons.

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

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

7.4.1 Risk/Benefit Assessment

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:

- Judge whether the anticipated benefit, either of new knowledge or of improved health or other direct benefit for the research subjects, justifies asking any person to undertake the risks; and
- Disapprove research in which the risks are judged unreasonable in relation to the anticipated benefits.

The assessment of the risks and benefits of proposed research involves a series of steps:

1. **Identify the risks** associated with the research, as distinguished from the risks of activities, diagnostic tests, treatments, or therapies the subjects would receive even if not participating in research;
2. **Determine whether the risks will be minimized** to the extent possible by evaluating the necessity of procedures that impart risk and whether the data could be gained by procedures that are already being performed for other purposes or by alternative procedures that impart less risk;
3. **Identify the anticipated benefits** to be derived from the research, both direct benefits to subjects and possible benefits to society, science and others;
4. **Determine whether the risks are reasonable in relation to the benefits**, if any, and assess the importance of the knowledge to be gained;

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 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 (e.g., the possible effects of the research on public policy) as among those research risks and benefits that fall within the purview of its responsibility.

7.4.1.1 Scientific or Scholarly Review

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

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

In making this determination, the IRB may draw on its own knowledge and expertise, or the IRB may draw on the knowledge and expertise of others, such as reviews by a funding agency, or departmental review. When scientific or scholarly review is conducted by an individual or entity external to the IRB, documentation that the above questions were considered must be provided to the IRB for review and consideration.

Scientific or scholarly review can be delegated to a departmental or other appropriate review committee.

7.4.2 Equitable Selection of Subjects

The IRB determines by reviewing the application, protocol/research plan and other materials that the selection of subjects is equitable with respect to gender, age, class, etc. The IRB will not approve a study that does not provide adequately for the equitable selection of subjects or has not provided an appropriate scientific and ethical justification for excluding classes of persons who might benefit from the research. In making this determination, the IRB evaluates:

- The purposes of the research;
- The setting in which the research occurs;
- Scientific and ethical justification for including vulnerable populations such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons;
- The scientific and ethical justification for excluding classes of persons who might benefit from the research; and
- The inclusion/exclusion criteria, and the procedures/materials intended for use for the identification and recruitment of potential subjects.

At the time of the continuing review the IRB will determine that the investigator has followed the subject selection criteria that was originally set forth at the time of the initial IRB review and approval.

7.4.2.1 Recruitment of Subjects

The investigator will provide the IRB with a plan for recruitment of all potential subjects. All recruiting materials will be submitted to the IRB, including advertisements, flyers, scripts, information sheets and brochures. The IRB should ensure that the recruitment plan and materials appropriately protect the rights and welfare of the prospective subjects (e.g., do not present undue influence). See Section 7.5.10 for a discussion of IRB review of advertisements and Section 7.5.11 for a discussion of IRB review of payments.

7.4.3 Informed Consent

The IRB will ensure that informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116 and 21 CFR 50.20. In addition, the IRB will ensure that informed consent will be

appropriately documented, in accordance with, and to the extent required by 45 CFR 46.117 and 21 CFR 50.27. The IRB will ensure, as part of its review, that the information in the consent document and process is consistent with the research plan, and, when applicable, the HIPAA authorization. See Section 11 below for detailed policies on informed consent.

7.4.4 Data and Safety Monitoring

For all research that is more than minimal risk, the investigator should submit a data and safety monitoring plan. The initial plan submitted to the IRB should describe the procedures for safety monitoring, reporting of unanticipated problems involving risks to subjects or others, descriptions of interim safety reviews and the procedures planned for transmitting the monitoring 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.

The IRB reviews the safety monitoring plan and determines if it makes adequate provision for monitoring the reactions of subjects and the collection of data to ensure the safety of subjects and address problems that may arise over the course of the study. If a plan was not submitted, the IRB determines whether or not a plan is required, and, depending on the circumstances, what the plan should include. The overall elements of the monitoring plan may vary depending on the potential risks, complexity, and nature of the research study.

The factors the IRB will consider in determining whether the safety monitoring plan is adequate for the research are as follows:

1. Monitoring is commensurate with the nature, complexity, size and risk involved.
2. Monitoring is timely. Frequency should be commensurate with risk. Conclusions are reported to the IRB.
3. For low risk studies, continuous, close monitoring by the study investigator or an independent individual may be an adequate and appropriate format for monitoring, with prompt reporting of problems to the IRB, sponsor and regulatory bodies as appropriate.
4. Data and Safety Monitoring plans should specify:
    - The entity or person(s) who will perform the monitoring, and the independence or affiliation that the entity or person(s) has with the sponsor or investigator
    - The safety information that will be collected and monitored, including serious adverse events and unanticipated problems
    - The frequency or periodicity of review of safety data
    - The procedures for analysis and interpretation of the data
    - The procedures for review of scientific literature and data from other sources that may inform the safety or conduct of the study
    - The conditions that trigger a suspension or termination of the research (i.e., stopping rules), if applicable

- The procedures for reporting to the IRB, including a summary description of what information, or the types of information, that will be provided

5. For a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), the plan should describe:
    - The composition of the board or committee. Generally, a DSMB should be composed of experts in all scientific disciplines needed to interpret the data and ensure subject safety. Clinical trial experts, biostatisticians, bioethicists, and clinicians knowledgeable about the disease/condition and treatment under study should be part of the monitoring group or be available if warranted.
    - Frequency and content of meeting reports
    - The frequency and character of monitoring meetings (e.g., open or closed, public or private)
    - The Charter should be provided, when one exists

In general, it is desirable for a DSMB or DMC to be established by the study sponsor for research that is blinded, involves multiple sites, involves vulnerable subjects, or employs high-risk interventions. For some studies the National Institutes of Health (NIH) require a DSMB. The IRB has the authority to require a DSMB or DMC as a condition for approval of research where it determines that such monitoring is needed. When DSMBs or DMCs are used, IRBs conducting continuing review of research may rely on a current statement, or the most recent report, from the DSMB or DMC which indicates that it has and will continue to review study-wide adverse events, study wide 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.

7.4.5 Privacy and Confidentiality

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

7.4.5.1 Definitions

Privacy. Having control over the extent, timing, and circumstances of sharing oneself (physically, behaviorally, or intellectually) with others. It is the state or condition of being free from unauthorized intrusion, being observed or disturbed by other people.

Confidentiality. Methods used to ensure that information obtained by investigators about subjects is not improperly divulged.

Private information. Information that 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).

Sensitive Information. Data or information, on any storage media or in any form or format, which requires protection due to the risk of harm that could result from inadvertent or deliberate disclosure, unauthorized access, misuse, alteration, or loss or destruction of the

information (e.g., could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation).

Identifiable information. Information where the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

7.4.5.2 Privacy

The IRB must determine whether the activities in the research appropriately protect the privacy of potential and actual subjects. In order to make that determination, the IRB must obtain information regarding how the investigators plan to access subjects or subjects' private, identifiable information and the subjects' expectations of privacy in the situation. Investigators must have appropriate authorization to access the subjects or the subjects' information.

In developing strategies for the protection of subjects' privacy, consideration is given to:

1. Methods used to identify and contact potential participants
2. Settings in which an individual will be interacting with an investigator
3. Appropriateness of all personnel present for research activities
4. Methods used to obtain information about participants, and the nature of the requested information including minimizing the information obtained to achieve the aims of the research
5. Information that is obtained about individuals other than the "target subjects," (e.g., a subject provides information about a family member for a survey) and whether such individuals meet the regulatory definition of "human subject"

7.4.5.3 Confidentiality

The IRB must determine if appropriate protections are in place to minimize the likelihood that information about subjects will be inappropriately divulged. Safeguards designed to protect confidentiality should be commensurate with the potential of harm from unauthorized, inappropriate or unintentional disclosure.

At the time of initial review, continuing review and with any requests for modification, the IRB assesses whether there are adequate provisions to protect data confidentiality. The IRB does this through the evaluation of the methods used to obtain, record, share, and store information about individuals who may be recruited to participate in studies and about subjects. The investigator will provide the IRB with a plan regarding the procedures to be taken to protect the confidentiality of research data and sensitive information. Additionally, the investigator will provide information regarding information security procedures and plans to address the protection of paper documents, other physical media (e.g., audio or videotapes), and electronic data and information including the use, maintenance, storage, and transmission of information. The IRB will review all information received from the investigator and determine whether or not the confidentiality of research data is sufficiently protected. In some cases, the IRB may also

require that a Certificate of Confidentiality be obtained to additionally protect research data (See Section 25.8).

In reviewing confidentiality protections, the IRB shall consider whether or not the data or other information accessed or gathered for research purposes is sensitive and 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, methods of transmission, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections. In reviewing confidentiality protections, the IRB shall also consider regulations and organizational requirements and policies regarding the use of information and information security.

Research regulated by the FDA that involves the use of electronic data collection/storage systems must comply with the requirements of 21 CFR Part 11.

7.4.6 Vulnerable Populations

Certain individuals, by nature of their age or mental, physical, economic, educational, or other situation, may be more vulnerable to coercion or undue influence than others. 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.

For an extensive discussion about the IRB's review and approval process for individual populations of vulnerable subjects, please refer to Section 12.

7.5 Additional Considerations

7.5.1 Determination of Risk

At the time of initial and continuing review, the IRB will make a determination regarding the risks associated with the research plan. Risk determinations may vary over the life of a research plan depending on the procedures and risks that subjects will be exposed to as the research progresses. The level of risk associated with the research influences eligibility for expedited review. The meeting minutes will reflect the convened IRB's determination regarding risk levels; expedited reviewers will document the determination of risk level on the reviewer's checklist.

7.5.2 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 study. All studies will be reviewed by the IRB at intervals appropriate to the degree of risk but no less than once per year. For research subject to the revised Common Rule, the IRB will conduct continuing review of research requiring review by the convened IRB at intervals appropriate to the degree of risk of the research, but not less than once per year, except as described in Section 7.7 In some circumstances, a shorter

review interval (e.g., semi-annually, quarterly, or after accrual of a specific number of participants) may be required (see below). The meeting minutes will reflect the convened IRB's determination regarding review frequency; expedited reviewers will document the determination of risk level on the reviewer's checklist.

7.5.3 Review More Often Than Annually

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

1. The probability and magnitude of anticipated risks to subjects.
2. The likely medical/psychological/social/legal/educational condition of the proposed subjects.
3. The overall qualifications of the investigator and other members of the research team.
4. The specific experience of the 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/unanticipated problems more likely.
7. The involvement of especially vulnerable populations likely to be subject to undue influence or coercion (e.g., terminally ill)
8. A history of serious or continuing non-compliance on the part of the investigator.
9. 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 one year unless the study does not require continuing review. If an approval period of less than one year is specified by the IRB for research that is subject to continuing review, the reason for more frequent review must be documented in the expedited reviewer's checklist.

7.5.4 Independent Verification That No Material Changes Have Occurred

The IRB recognizes that protecting the rights and welfare of subjects sometimes requires that the IRB use sources other than the investigator to independently verify that no material changes have occurred since previous IRB review.

The IRB will determine the need for verification from outside sources on a case-by-case basis. The following factors will be considered when determining which studies require independent verification:

1. The probability and magnitude of anticipated risks to subjects.

2. The likely medical/psychological/social/legal/educational condition of the proposed subjects.
3. The probable nature and frequency of changes that may ordinarily be expected in the type of research proposed.
4. Concern about possible material changes occurring without IRB approval have been raised based on information provided in continuing review reports or from other sources.
5. Investigators who have previously failed to comply with federal regulations and/or the requirements or determinations of the IRB.
6. Research without a routine monitoring plan.
7. Any other factors the IRB deems verification from outside sources is relevant.

In making determinations about independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period, or may require such verification at the time of continuing review, review of modification requests and/or unanticipated problems.

If any material changes have occurred without IRB review and approval, the IRB will decide the corrective action to be taken (see Section 16 on Non-compliance).

7.5.5 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 (e.g., 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:

1. High risk studies;
2. Studies that involve particularly complicated procedures or interventions;
3. Studies involving highly vulnerable populations (e.g., ICU patients, children who are wards);
4. Studies involving study staff with minimal experience in administering consent to potential study participants; or
5. Other situations when the IRB has concerns that consent process may not be/is not being conducted appropriately (e.g., prior investigator non-compliance, etc.).

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 RIO Manager will develop a monitoring plan and submit it to the IRB for approval. The consent monitoring

will be conducted by a member of the Corporate Compliance audit team or another party, either affiliated or not with HMH. The investigator will be notified of the IRB's determination and the reasons for the determination. Arrangements will be made with the investigator for the monitoring of the consent process, typically for a specified number of subjects. When observing the consent process, the monitor will determine:

- Whether the informed consent process was appropriately conducted 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.

7.5.6 Investigator Qualifications

The IRB may review credentials, curriculum vitae, resumes, or other relevant materials to determine whether investigators and members of the research team are appropriately qualified to conduct the research. The IRB relies upon other HMH credentialing processes to inform this determination.

7.5.7 Conflicts of Interest (COI)

Investigator Conflicts of Interest

The IRB research application asks specific questions regarding the investigator and research team compliance with disclosure requirements and whether or not any COI management plans are in place. As part of its review process, the IRB will make a final determination as to whether any conflict of interest is adequately addressed and protects the human subjects in the research.

Institutional Conflicts of Interest

As with individual conflict of interest, the IRB has final authority to determine whether the Institutional Conflict, the Financial Interest, and the management plan, if any, allow the study to be approved. Significant New Findings

During the course of research, significant new knowledge or findings about the research, the test article, and/or the condition under study may develop. The investigator 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. Because 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 investigator contact the currently enrolled subjects to inform them of the new information. The IRB will communicate this requirement to the investigator. If the study is still enrolling subjects, the consent document should be updated. IRB may require that the currently enrolled subjects be re-consented or otherwise provided with the new information. The IRB may also require that former subjects be provided with the new information, e.g., if it impacts their rights or welfare.

7.5.8 Advertisements and Recruitment Materials

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

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

This information should be submitted to the IRB with the initial application or, if recruitment is proposed after study approval, as a modification request.

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

1. Statements implying a certainty of favorable outcome or other benefits beyond what was outlined in the consent document and the research plan.
2. Claims, either explicitly or implicitly, that the test article (drug, biologic or device) is 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. Offers for a coupon good for a discount on the purchase price of an investigational product once it has been approved for marketing.
8. The inclusion of exculpatory language.

Recruitment materials 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 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.

Once approved by the IRB, an advertisement cannot be altered or manipulated in any way without prior IRB approval.

Directory listings of research such as ClinicalTrials.gov are not considered advertisements and therefore do not require IRB review and approval if the listing is limited to the following basic trial information: title, purpose of the study, research plan summary, basic eligibility criteria, study site location(s), and how to contact the study site for further information.

The first contact prospective study subjects make is often with a person who follows a script to determine basic eligibility for the specific study. The IRB should assure the procedures followed adequately protect the rights and welfare of the prospective subjects.

7.5.9 Payments 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 unduly influencing subjects. The amount of compensation must be proportional to the time and inconveniences posed by participation in the study.

Investigators who wish to pay research subjects must submit to the IRB the amount and schedule of all payments. Investigators should indicate in their research project application the justification for such payment. Such justification should substantiate that proposed payments are reasonable and commensurate with the expected contributions of the subject and do not constitute (or appear to constitute) undue pressure on the potential subject to volunteer for the research study.

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

Credit for payment should be prorated 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 could unduly induce subjects to remain in the study when they otherwise would have withdrawn.

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

Unless the study is confidential, HMH Finance Department requires identifying information to issue checks, cash, or gift certificates to subjects. The consent form must inform subjects that they will be asked to provide their Social Security Number and verification of U.S Citizenship or Permanent Resident Status to receive payment. For confidential studies, only name and address are required by the Finance Department, but the investigator MUST keep an identity key in a secure place.

7.5.10 Non-Monetary Gifts and Incentives

Similar to financial incentives, non-monetary gifts or incentives can also present problems of undue influence or coercion that impact a potential subject's ability to fully and freely consider participation in research.

If subjects will be provided with non-monetary gifts or tokens of appreciation, such as totes, books, toys, or other such materials, the approximate retail value must be described to the IRB and the IRB will be provided with a description, photo, or sample product to review.

The IRB will review all gifts and incentives being particularly sensitive to the influence of power or authority, whether perceived or actual, over free decision-making. Overt coercion (e.g., threatening loss of credit, or access to services or programs, to which the potential subjects are otherwise entitled) is never appropriate. Moreover, it must be clear that choosing to not participate will not adversely affect an individual's relationship with the organization or its staff or the provision of services in any way (e.g., loss of credits or access to programs).

Investigators should carefully structure incentives and methods of disbursement so that while the incentives may serve as a factor in a subjects decision to participate, that they have not served to unduly influence or coerce participation.

7.5.11 State and Local Laws

The IRB considers and adheres to all applicable state and local laws in the jurisdictions where the research is taking place. The HRPP and IRB rely on HMH Counsel for the interpretation and application of New Jersey law and the laws of any other jurisdiction where research is conducted as they apply to human subjects research. The IRB will ensure that consent forms are consistent with applicable state and local laws.

7.6 Possible IRB Actions

Approval. The research, proposed modification to previously approved research, or other item is approved. The IRB has made all of the determinations required for approval (i.e., approval criteria and any applicable special determinations (e.g., waivers, alterations, vulnerable population determinations, etc.). No further action is needed.

Conditions Required for Approval. The research, proposed modification to the previously approved research, or other item is approved but conditions must be satisfied before the approval becomes effective.

The IRB may approve research with conditions if, given scope and nature of the conditions, the IRB is able, based on the assumption that the conditions are satisfied, to make all of the determinations required for approval (i.e., approval criteria and any applicable special determinations (e.g., waivers, alterations, vulnerable population determinations, etc.)). Any time the IRB cannot make one or more of the determinations required for approval, the IRB may not approve the study with conditions.

The IRB may require the following as conditions of approval of research:

1. Confirmation of specific assumptions or understanding on the part of the IRB regarding how the research will be conducted (e.g., confirmation that research excludes children);
2. Submission of additional documentation (e.g., certificate of training);
3. Precise language changes to the study, consent, or other study documents; or
4. Substantive changes to the study, consent, or other study documents along with clearly stated parameters that the changes must satisfy.

When the IRB approves research with conditions, the conditions will be documented in the IRB minutes for research reviewed at a convened meeting or in the Reviewer Checklist for research reviewed under an expedited review procedure.

When the convened IRB approves research with conditions, the IRB may designate the IRB Chair (and/or other qualified individual(s)) to review responsive materials from the investigator and determine that the conditions have been satisfied. If the conditions have not been satisfied, or are only partially satisfied, the responsive materials must be referred to the convened IRB for review. When an expedited reviewer approves research with conditions, the original expedited reviewer (and/or other qualified individual(s)) will receive the response materials.

After verification, the following will be documented in IRB records and written communication to the investigator:

- The date when verification was made that all IRB conditions have been satisfied (i.e., the "effective date");
- For initial approval, the date when approval becomes effective (i.e., the date on which the investigator's response has been accepted as satisfactory), and;
- The date by which continuing review must occur.

The IRB will be informed of the outcome of the review of the investigator's response.

Partial Approval. The IRB may stipulate that certain components of the research, which the IRB has determined to meet the criteria for approval, may commence or continue while other components of the research that require modification or clarification cannot begin or continue until the outstanding issues are resolved and approved by the convened IRB. For example, the

IRB could determine that a study may begin but that children cannot be enrolled until the investigator submits, and the IRB approves, a plan for assent.

Deferred. This action is taken by the IRB when modifications are required (of the nature or amount that the full IRB cannot make or specify exact changes or parameters), or additional information or clarification is needed in order to determine that one or more criteria for approval are satisfied (e.g., the risks and benefits cannot be assessed with the information provided).

The deferral and the basis for the deferral is documented in the IRB minutes (for convened review) or Reviewer Checklist (for expedited review) and is communicated to the investigator in writing.

When the convened IRB defers approval, the responsive materials from the investigator will be provided to the convened IRB for review at a subsequent meeting. When an expedited reviewer defers approval, the original expedited reviewer will review the response materials whenever possible. In the event that the original expedited reviewer is unavailable, the response will be reviewed by the IRB Chair or other qualified IRB member who has been designated to conduct expedited review.

Disapproved. The IRB may determine that the proposed research cannot be conducted at HMH or by employees or agents of HMH or otherwise under the auspices of HMH. Disapproval can only be decided at the convened IRB meeting. An expedited reviewer cannot disapprove a study.

Approval in Principle. As per federal regulations, [45CFR46.118], there are circumstances in which a sponsoring agency may require certification of IRB approval as a condition of submitting for or releasing funds but before definitive plans for the involvement of human subjects have been developed (e.g., certain training grants or grants in which the procedures involving human subjects are dependent on the completion of animal studies or instrument development). In these circumstances, the IRB may grant "approval in principle" without having reviewed the as yet undeveloped procedures or materials. The IRB Chair or designee will review the available information (i.e., the grant or proposal and any supplemental information provided by the investigator) and, if appropriate, will provide certification of IRB approval in principal. If the proposal is funded, the 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.

7.7 Continuing Review

For research subject to the 2018 Common Rule (the revised Common Rule), the IRB will conduct continuing review of ongoing research requiring review by the convened IRB at intervals that are appropriate to the level of risk of the research, but not less than once per year, except as described below. The date by which continuing review must occur will be recorded in the IRB electronic system and on initial and continuing review approval letters.
Unless an IRB determines otherwise, continuing review of research subject to the 2018 Common Rule (the revised Common Rule) is not required in the following circumstances:

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

HMH IRB's may determine that continuing review is required for any research protocol that falls within the above criteria. For example, the IRB may determine that continuing review is required when:

1. Required by other applicable regulations (e.g., FDA);
2. Required by the terms of a grant, contract, or other agreement
3. The research involves topics, procedures, or data that may be considered sensitive or controversial;
4. The research involves particularly vulnerable subjects or circumstances that increase subjects' vulnerability;
5. An investigator has minimal experience in research or the research type, topic, or procedures; and/or
6. An investigator has a history of noncompliance

When the HMH IRB determines that continuing review is required for such research, it will document the rationale in the IRB record and communicate the requirement to the investigator in the IRB determination letter.

Once the study will no longer be subject to annual continuing review, a yearly check in will be required in its place. The annual check in will be used to ensure institutional requirements continue to be met (e.g., verification of human subjects training, COI review) and to ensure the status of the study (e.g. open or closed, enrolling).

There is no exception to the requirement for continuing review in FDA regulations. The IRB will conduct continuing review of ongoing FDA-regulated research, and any research where it is required by applicable regulations, policy, or other requirements (e.g., as a condition of funding or contractually), at intervals that are appropriate to the level of risk of the research, but not less than once per year, as long as the research remains active. The date by which continuing review must occur will be recorded in the IRB electronic system and on initial and continuing review approval letters.

7.7.1 Approval Period

At the time of initial review and at continuing review, the IRB will make a determination regarding the frequency of review of the research study. All studies will be reviewed by the IRB

at intervals appropriate to the degree of risk but no less than once per year. In some circumstances, such as when the research involves a high likelihood or severity of risks, when the research imparts significant risks without likelihood of direct benefit, or when the research population is especially vulnerable, a shorter review interval (e.g., semi-annually, quarterly, or after accrual of a specific number of participants) may be required (see below). Or, for a new investigator or an investigator who has recently had a study suspended by the IRB due to regulatory concerns, an on-site review by a subcommittee or designee 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 convened IRB review, the meeting minutes will reflect the IRB's determination regarding review frequency. For expedited review, the determination will be documented in the Reviewer's Checklist.

IRB approval is considered to have lapsed at midnight on the expiration date of the approval. For a new study reviewed by the IRB, the approval commences on the date that the IRB conducts its final review of the study; that is, the date that the convened IRB or expedited reviewer approves the research **or** the date ("effective date") that it is verified that the requirements of the IRB have been satisfied following an action of Approval with Conditions. 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 the effective date of initial IRB approval.

The use of the effective date of IRB approval to determine the latest permissible date for continuing review *only applies to the first continuing review*. For all subsequent continuing reviews of a research study subject to convened board review, the date the convened IRB or the date that the expedited reviewer conducts continuing review and approves the study (with or without conditions) determines the latest permissible date of the next continuing review.

The approval date and approval expiration date are clearly noted on IRB determination letters and must be strictly adhered to. Investigators should allow sufficient time for development and review of continuing review submissions.

IRB review of a proposed modification to research ordinarily does not alter the date by which continuing review must occur. This is because continuing review is review of the full research project, 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. If the IRB performs continuing review within 30 days before the IRB approval period expires, the IRB may retain the anniversary date as the date by which the continuing review must occur.

7.7.2 Continuing Review Process

As a courtesy to investigators, the IRB Office staff will send out renewal notices to investigators at 90 days, 60 days, 30 days and daily thereafter in advance of the expiration date; however, it is the investigator's responsibility to ensure that the continuing review of ongoing research is approved prior to the expiration date. By federal regulation, no extension to that date can be granted.

Investigators must submit the following for continuing review:

1. The initial study application form updated with any changes (this serves as the protocol/research plan summary);
2. The current protocol/research plan;
3. The current Investigator's Brochure or other updated risk information (if applicable);
4. The most recent report from the DSMB or DMC (if applicable);
5. The most recent multi-center progress report (if applicable);
6. Any proposed modifications to the protocol/research plan, consent, or study; and
7. The continuing review application form (progress report)
8. Reports of any internal audits by Corporate Compliance (if not already reviewed by the IRB)

IRB Office staff attend the convened meetings and bring the complete study files for each study on the agenda. IRB members can request the study file or any additional materials from the IRB staff prior to the meeting.

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

7.7.3 Approval Considerations

In order to re-approve research at the time of continuing review, the IRB must determine that the regulatory criteria for approval continue to be satisfied. Because the research was previously found to satisfy the criteria for approval, the IRB focuses its considerations at the time of continuing review on whether any new information is available that would affect the IRB's prior determination that the criteria for approval are satisfied. The IRB pays particular attention to four aspects of the research:

1. Risk assessment and monitoring;
2. Adequacy of the informed consent process; including that the current consent document is still accurate and complete and any significant new findings that arise from the review process and that might relate to participants' willingness to continue participation will be provided to participants.;
3. Local investigator and organizational issues; and
4. Research progress.

7.7.4 Convened Board Review

In conducting continuing review of research not eligible for expedited review, all IRB members are provided with access to all of the materials listed in Section 7.7.2 and are responsible for reviewing the project summary, the current consent document, the progress report, and, if applicable, the data and safety monitoring report, multi-center study progress reports, and any

proposed modifications to the protocol/research plan, or consent. The Primary Reviewer is responsible for reviewing the complete materials submitted for continuing review including the complete research plan and is given access to the complete IRB file and relevant IRB meeting minutes.

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

7.7.5 Expedited Review

In conducting continuing review under expedited procedures, the reviewers receive all of the previously noted materials. The reviewer(s) complete the **Study Review** checklist to determine whether the research meets the criteria allowing continuing review using the expedited procedure, and if so, whether the research continues to meet the regulatory criteria for approval (See Section 7.7.3 Approval Considerations).

If the research subject to the 2018 Common rule (the revised Common Rule) no longer requires continuing review and the IRB reviewer determines that continuing review is required, the reviewer shall document the rationale in the checklist.

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 unless it has progressed to the point that it involves only one or both of the following:

- Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
- Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care;

and in limited circumstances described by expedited review categories (8) and (9) (see Expedited Review Categories in Section 7.2.1). It is also possible that research activities that previously qualified for expedited review, have changed or will change, such that expedited IRB review would no longer be permitted for continuing review.

7.7.6 Possible IRB Actions after Continuing Review

As with Initial Review, at the time of Continuing Review, the Convened IRB or IRB Member(s) conducting expedited review may take any of the following actions (see Section 7.6 for a detailed description of these actions):

1. Approval
2. Conditions Required for Approval
3. Deferred

Additionally, the convened IRB may vote to disapprove the study. If an IRB member conducting expedited review believes that the study should be disapproved, it will be referred to the convened board for review. If the IRB has significant concerns, the IRB may vote to suspend or terminate the research (See Section 8 for a detailed discussion of suspensions and terminations).

If a research study receives Approval with Conditions at the time of the Continuing Review, the IRB will specify whether any conditions need to be satisfied before an investigator can continue particular research activities related to those conditions or requirements that must be adhered to until the conditions of approval have been satisfied. For example, if at the time of continuing review, the IRB requires the investigator to change the research protocol to include a specific new procedure for screening prospective subjects, the IRB could approve the research with the following condition: research activities involving currently enrolled subjects may continue, but no new subjects may be enrolled until a designated IRB member reviews a revised protocol and verifies that the protocol includes the new screening procedure. Additionally, the IRB may specify a time period, such as 1, 2, or 3 months, for the condition/s to be satisfied as long as the activity with conditions is not begun/restarted until approval is granted.

7.7.7 Lapses 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 re-approval does not occur within the time set by the IRB, all research activities must stop, including recruitment (media advertisements must be withdrawn), enrollment, consent, interventions, interactions, and data collection. **This will occur even if the investigator has provided the continuing information before the expiration date. Therefore, investigators must submit their continuing review materials enough in advance of expiration to allow sufficient time for IRB review before the expiration date**.

The lapse of IRB approval due to a failure to complete continuing review and obtain re-approval prior to expiration of the prior approval does not ordinarily constitute a suspension or termination of IRB approval, for federal reporting purposes; however, the failure to meet continuing review obligations may be grounds for suspension or termination of the research. If the IRB notes a pattern of non-compliance with the requirements for continuing review (e.g., an investigator repeatedly or deliberately neglects to submit materials for continuing review in a timely fashion or the IRB itself is not meeting the continuing review dates), the IRB should determine the reasons for the non-compliance and take appropriate corrective actions. The IRB must report to FDA/OHRP any instance of serious or continuing non-compliance with FDA regulations or IRB requirements or determinations.

When the IRB approves research with conditions, if the research expires/lapses before the conditions are reviewed and approved, all research activities must stop until approval is obtained. The IRB Office is responsible for notifying the investigator of the expiration of approval and that all research activities must stop.

However, the IRB recognizes that, while enrollment of new subjects cannot occur after the expiration of IRB approval, temporarily continuing participation of already enrolled subjects may be necessary or appropriate, for example, when the research interventions hold out the prospect of direct benefit to the subjects, or when withholding those interventions or safety monitoring procedures, would place subjects at increased risk. In these instances, the investigator should, at the earliest opportunity, contact the IRB office and submit a request to continue those research activities that are in the best interests of subjects. Such a request should specifically list the research activities that should continue, and provide justification, and indicate whether the request applies to all or only certain subjects. The IRB Chair or designee will review the request and provide a determination regarding what activities, if any, may continue during the lapse. Such a determination may include a time limit or other conditions or restrictions. If the IRB decides that already enrolled subjects should continue to receive the interventions that were being administered to subjects under the research project, data collection (especially safety information) should also continue for such subjects.

When there is insufficient time to obtain an IRB determination (e.g., the study regimen includes daily administration of an investigational agent), the investigator may make an initial determination, in consultation with the subjects' treating physician, if appropriate. In such cases, the investigator must, as soon as possible, contact the IRB office and submit a request for confirmation that the IRB agrees with the determination. The IRB Chair or designee will review the request and provide a determination. In the event that the IRB does not agree with the investigator's determination, or only agrees in part (e.g., agrees that some but not all of the activities are in the best interests of subjects), the IRB will notify the investigator who must then comply with the IRB's requirements or request a re-review of the determination by providing additional justification or information that the IRB may not have considered.

The study will be closed administratively after 60 days. If the investigator wishes to re-open the study, full board review will be required.

7.8 Modification of an Approved Protocol

Investigators may wish to modify or amend their approved applications. **Investigators must seek IRB approval before making any changes, no matter how minor, 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 hazards to the subject (in which case the IRB must then be notified at once).

Modifications may be permanent (Protocol Modification) which make changes to the protocol for all remaining subjects or for temporary circumstances (Protocol Exceptions) in which the specific procedures called for in a protocol are not in the best interests of a specific patient(s)/subject(s) (examples: patient/subject is allergic to one of the medications provided as supportive care; patient/subject is not eligible in a direct benefit study). Usually an Exception is a change that is planned and has prior agreement from the sponsor. See Section 7.8.5 for details on Protocol Exceptions.

Investigators should consider whether the proposed changes to the research alter the original scope, purpose, or intent of the research. When the research itself is fundamentally changed, the IRB will typically require a new study application rather than allow such changes to be made through a modification to the existing research plan.

7.8.1 Procedures

Investigators must submit documentation to inform the IRB about the proposed changes to the study, including, but necessarily limited to:

- Revised protocol/research plan, application, and/or study materials (in tracked changes or with a detailed summary of changes and the locations of those changes);
- Revised consent/parental permission/assent documents (if applicable) or other documentation proposed to be provided to subjects when the proposed change(s) to the research might relate to their willingness to continue to participate in the study; and
- Any other relevant documentation provided by the sponsor or coordinating center.

IRB Office staff will review the submission and make an initial determination whether the proposed changes may be approved through an expedited review process, if the changes are minor, or whether the modification warrants convened 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 research study for convened board review.

7.8.2 Convened Board Review of Modifications

When a proposed change in a research study is not minor, 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 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 provided and review all documents provided by the investigator.

At the meeting, the Primary Reviewer presents an overview of the proposed modifications and assists the IRB Chair in leading the IRB through the completion of the regulatory criteria for approval. The IRB will also determine whether the research with the proposed modifications continues to meet the regulatory criteria for approval.

When the IRB reviews modifications to previously approved research, the IRB considers 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 future/current/past participants.

7.8.3 Expedited review of 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 experienced designee(s) among the IRB members.

The reviewer will also consider whether information about those modifications might relate to future/current/past participants' willingness to continue to take part in the research and if so, whether to provide that information to participants.

7.8.4 Possible IRB Actions after Modification Review

As with Initial Review, at the time of Continuing Review, the Convened IRB or IRB Member(s) conducting expedited review may take any of the following actions (see Section 7.6 for a detailed description of these actions):

1. Approval
2. Conditions Required for Approval
3. Deferred

Additionally, the convened IRB may vote to disapprove the proposed changes. If an IRB member conducting expedited review believes that the proposed modifications should be disapproved, they will refer the proposed modification to the convened board for review. If the proposed changes raise significant concerns on the part of the IRB, the IRB may vote to suspend or terminate the research (See Section 8 for a detailed discussion of suspensions and terminations).

7.8.5 Protocol/Research Plan Exceptions

Protocol/Research Plan exceptions are circumstances in which the investigator wishes to deviate from eligibility criteria or one or more of the specific procedures called for in a research plan. Unlike modifications that apply to all subsequent subjects in the research, a protocol/research plan exception only applies to a specific subject or group of subjects.

Exceptions are planned, and the investigator gets approval from the sponsor and the IRB ahead of time. For sponsored research, prior approval from the sponsor is generally required. Depending on the nature of the exception, an expedited review is possible. To be approved under expedited review, exceptions must not increase risk or decrease benefit, change the risk/benefit analysis, negatively affect the participant's rights, safety, welfare, or negatively affect the integrity of the resultant data. Review of exceptions that represent more than minor changes or risks levels greater than minimal must be done at a convened meeting of the IRB.

Procedures for exceptions are the same as for a Protocol Modification. The investigator must submit a "Modification Request Form" along with any revised documentation to be presented to the subject(s) and documentation of sponsor approval, if applicable.

The only time a protocol/Research Plan exception would not require prior sponsor or IRB approval is when the exception is necessary to avoid an immediate hazard to the participant. In such cases, the exception must be submitted to the IRB as soon as possible.

7.9 Closure of Research Studies

The completion or early termination of the study is a change in activity and must be reported to the IRB. Although subjects will no longer be "at risk" under the study, a final report to the IRB allows it to close its files as well as provides information that may be used by the IRB in the evaluation and approval of related studies.

Studies may be closed when the involvement of human subjects ceases (interventions, interactions, observations, and the gathering, use, study, and analysis of identifiable private information, including specimens, are all complete). Studies may be closed when the only remaining research activity involves the analysis of unidentifiable individual level data, or aggregate data sets.

For multi-center research, the study may be closed once all research activities (as above) are complete at HMH and any sites for which the IRB is the “IRB of record”. If the investigator is serving as the lead investigator or HMH is the coordinating center, please note that the study must remain open as long as the coordinating center is still receiving, studying, using, or analyzing identifiable private information from other sites (even if local interventions, interactions, observations, and data gathering is complete).

Investigators must submit study closures to the IRB. With closure submissions, the investigator must provide a summary of the research activity and any findings available at that time.

Investigators may maintain the data that they collected, including identifiable private data, if this is consistent with the IRB-approved research plan. However, investigators may not conduct any additional analysis of identified data without re-applying for IRB approval. Investigators must continue to protect the confidentiality of the data as described to the IRB and honor any other commitments that were agreed to as part of the approved research including, for example, future use of data or specimens, provision of research results to subjects, and provision of any outstanding payments or compensation.

The IRB will review study closure reports, typically by expedited review, and either approve the closure of the study or request additional information or confirmation of facts from the investigator.

7.10 Reporting IRB Actions

All IRB actions are communicated to the investigator, and/or designated contact person for the research study, in writing within ten (10) working days via a template letter prepared by the IRB staff. For an approval, along with written notification of approval, a copy of the approved consent/assent/permission form/s (if applicable) containing the IRB stamp with the dates of the approval and expiration (if applicable) will be sent to the investigator. For approval with conditions, the notification will include a listing of the conditions that must be satisfied. For a

deferral, the notification will include the modifications and/or clarifications required along with the basis for requiring those modifications. For a disapproval, termination or suspension, the notification will include the basis for making that decision and give the investigator an opportunity to respond in person or in writing.

The IRB reports its findings and actions to the organization in the form of its minutes, which are distributed by IRB staff to the HMH Institutional Official.

7.11 Failure to Respond

Failure to submit a response to IRB requirements within 60 days of the IRB date of determination may result in administrative closure of the IRB file (for new study submissions). When research has IRB approval, and an investigator fails to respond to requirements related to a subsequent submission (e.g., a request for modification), the RIO Manager will review the circumstances, including any potential impact on human subjects, and will contact the investigator to try to secure a response. If the investigator continues to be unresponsive, the failure of the investigator may be considered non-compliance and will be reviewed in accordance with the procedures in Section 16. The investigator will receive notification, including an explanation. An extension beyond 90 days may be granted by the IRB if sufficient cause is provided by the investigator.

7.12 Appeal of IRB Decisions

When an IRB research study is disapproved or deferred, the IRB will notify the investigator in writing about the specific deficiencies and the modifications that are necessary for appropriate IRB approval. The IRB shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing. Similarly, when research is suspended in part or in full, or terminated, the IRB will notify the investigator in writing of the suspension or termination and the reasons for its decision.

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

Because the IO is responsible for policies and procedures followed by the IRB, the IO may review IRB decisions to ensure that the decision-making process is appropriate. If the IO has concerns regarding the process that the IRB has followed in making a decision, he/she may request that the IRB reconsider the decision. However, the IO cannot overrule an IRB decision.

7.13 Research Previously Approved By Another IRB

When an investigator transfers research to HMH that was previously approved by another IRB, the investigator must submit the research for review under the procedures covered by this

section. No research activity may take place under HMH auspices without the appropriate review and approval.

Research approved as exempt at the previous institution will be reviewed according to the procedures in Section 6. All other research must be submitted as if it were undergoing initial review and will be reviewed under expedited review or by the convened IRB. Research that solely involves the analysis of existing identifiable data may be considered under Expedited Review Category 5.

For research transfers where stopping research interventions might harm subjects, the investigator can request permission from the IRB to continue research interventions under the oversight of the prior organization's IRB until final HMH approval is obtained.

8 Study Suspension, Termination and Investigator Hold

8.1 Suspension/Termination

IRB approval may be suspended or terminated if research is not being conducted in accordance with IRB or regulatory requirements or has been associated with unexpected problems or serious harm to subjects. (See Section 15 for a discussion of unanticipated problems and Section 16 for a discussion of non-compliance.) The IRB's authority to suspend or terminate research applies to all research subject to IRB approval, including exempt research with limited IRB review and research for which continuing review is no longer required. **Suspension** of IRB approval is a directive of the convened IRB or IRB Chair to temporarily stop some or all previously approved research activities. Suspensions made by the IRB Chair must be reported to a meeting of the convened IRB. Suspended research studies remain open and require continuing review. Investigators must continue to provide reports on adverse events and unanticipated problems to both the IRB and sponsors just as if there had never been a suspension (i.e., all events that need to be reported during a study need to continue to be reported during the suspension period).

When approval of some or all research activities is suspended by the IRB, the IRB will consider notification of subjects and any actions necessary to ensure that the rights, safety, and welfare of subjects are appropriately protected.

The IRB shall notify the investigator in writing of suspensions and shall include a statement of the reasons for the IRB's actions and any requirements or conditions associated with the suspension (e.g., notification of subjects). The investigator shall be provided with an opportunity to respond in person or in writing.

Suspensions of IRB approval must be reported promptly to the IO, Chief Compliance Officer, Vice-President of Research, sponsors including federal department or agency heads, and federal oversight agencies according to applicable federal and organizational requirements. See Section 14 for a detailed discussion of reporting requirements.

Termination of IRB approval is a directive of the convened IRB to permanently stop all activities in a previously approved research study. Terminated research studies are closed and no longer require continuing review. Terminations of IRB approval of research studies must be made by the convened IRB.

When study approval is terminated by the IRB, in addition to stopping all research activities, the IRB will consider notification of subjects and any actions necessary to ensure that the rights, safety, and welfare of subjects are appropriately protected.

The IRB shall notify the investigator in writing of a study termination and shall include a statement of the reasons for the IRB's actions and any requirements associated with the termination (e.g., notification of subjects). The investigator shall be provided with an opportunity to respond in person or in writing.

Terminations of IRB approval must be reported promptly to the IO, Chief Compliance Officer, Vice-President of Research, the Department Chair of the PI's department, sponsors including federal department or agency heads, and federal oversight agencies according to applicable federal and organizational requirements. See Section 14 for a detailed discussion of reporting requirements.

***Note*:** Suspension or termination of research studies approved by the IRB can also be issued by Organization officials acting outside of and unrelated to the interests of the IRB (i.e., not necessarily related to protecting the rights and welfare of study participants). Such Organization actions can be made by, for example, the IO, VP and Chief Compliance Officer, President, Provost, and Deans. The investigator must report any suspension or termination of the conduct of research by organization officials to the IRB. The IRB will then determine if suspension or termination of IRB approval is warranted.

8.2 Investigator Hold

An investigator may request an investigator hold when the investigator wishes to temporarily or permanently stop some or all approved research activities. Such a hold is initiated by an investigator, but must be immediately reported to the IRB so that the IRB can consider whether any additional actions are necessary to protect subjects. Investigator holds are not equivalent to IRB suspensions or terminations.

8.2.1 Procedures

1. Investigators must notify the IRB in writing that:
    a. They are voluntarily placing a study on hold
    b. A description of the research activities that will be stopped
    c. Proposed actions to be taken to protect current participants
    d. Actions that will be taken prior to IRB approval of proposed changes in order to eliminate apparent immediate risk of harm

2. Upon receipt of written notification from the investigator, the RIO Manager places the research on the next available agenda for review.
3. The IRB Chair and/or Manager, in consultation with the investigator, determines whether any additional procedures need to be followed to protect the rights and welfare of current participants as described in "Protection of currently enrolled participants"(see Section 8.3).
4. The IRB Chair and/or Manager, in consultation with the investigators, determine how and when currently enrolled participants will be notified of the hold.
5. Investigators may request a modification of the research on hold by submitting a request for a modification to previously approved research.

8.3 Protection of Currently Enrolled Participants

Before a study hold, termination, or suspension is put into effect the Chair, Manager, or IRB considers whether any additional procedures need to be followed to protect the rights and welfare of current participants. Such procedures might include:

- Transferring participants to another investigator/site
- Making arrangements for clinical care outside the research
- Allowing continuation of some research activities under the supervision of an independent monitor
- Requiring or permitting follow-up of participants for safety reasons
- Requiring adverse events or outcomes to be reported to the IRB and the sponsor
- Notification of current participants
- Notification of former participants

9 Off-site IRB Policies and Procedures

9.1 Independent IRB and/or Central IRB

HMH investigators wishing to conduct research may choose between the IRB services provided locally by HMH's IRB or those provided by another IRB (assuming the sponsor of the study has not designated the mandated IRB of record). While the institution has master reliance agreements with Western Institutional Review Board (WIRB), Central Institutional Review Board (CIRB), Advarra IRB, and Georgetown IRB, any IRB may be used pending the review of that IRB by the Reliance Analyst.

9.1.1 Investigator Responsibilities

1. Prior to submitting the application package to the external IRB, the investigator must satisfy HMH's application requirements for externally reviewed studies (abbreviated application form). The following actions must be completed and submitted to HMH's Office of Research Integrity:
    a. Departmental sign-off of the research in the electronic application
    b. Study Personnel must complete HMH COI and training requirements
    c. Upload copy of external IRB application
    d. Upload Sponsor Protocol/research plan document; and
    e. Upload draft consent document.
2. If using an external IRB, confirm with the sponsor that the sponsor will accept direct invoicing from the external IRB and allow direct payments to external IRB.
3. If using an external IRB, the investigator completes the IRB's-required materials by uploading all IRB required study documents, into the electronic submission system. The study team will convert the Sponsor's Consent Document into the HMH approved consent document.

9.1.2 HMH Responsibilities Prior to Accepting External Oversight for a Study

When the submission packet is received, the Reliance Analyst reviews the materials, and sponsor protocol/research plan. The following is reviewed:

- Eligibility to use external IRB review (industry-sponsored, industry-initiated)
- Review of investigator and study staff (confirmation of training/credentialing, assessment of prior non-compliance or other issues)
- Fee Invoice Authorization Form (if applicable)
- Departmental Chair/committee scientific merit sign off

- Involvement of special populations, e.g., minors/minor assent, adults unable to consent form themselves

Once the above are reviewed by the Reliance Analyst and is determined to be acceptable, the investigator will be notified that they may move forward with their submission to the external IRB. Concurrent with this notification is request for required confirmation from the investigator that organizational processes for financial disclosure/ COI management requirements, budget review and contract negotiation, and other required committee or ancillary reviews are either in process or completed. Appropriate Organization officials are copied on the notification for tracking and compliance purposes. Additional reminders of local policies concerning special topics (assent, incapacitated adults, etc.) may also be included in the notification.

9.1.3 HMH Responsibilities: Post External IRB Approval

HMH retains certain on-site responsibilities for all studies reviewed by any external IRB. Reports of site monitoring activities which have any findings that potentially impact human subject protections must be shared between the external IRB and HMH.

Investigators approved through external IRB review must still report local unanticipated problems, complaints, non-compliance, and an annual and end of study summary to the HMH IRB Office in compliance with HMH policy, in addition to any external IRB reporting requirements. Changes in study personnel must be submitted to HMH IRB via an updated Study Personnel Form **prior** to the personnel assuming any study responsibilities. Submission to HMH IRB for changes in study personnel must be submitted to and acknowledged by the Research Integrity Office prior to being submitted to the external reviewing IRB.

9.2 National Cancer Institute's Central IRB Adult and Pediatrics Initiative

HMH is a participant in the National Cancer Institute's Central Institutional Review Board (CIRB) Initiative for cooperative group protocols/studies that have been reviewed and approved by the CIRB. The HMH Research Integrity Office submits the necessary documentation to maintain institutional registration with the CIRB, including the "Authorization Agreement/Division of Responsibilities", the listing of Key Personnel, and the "Annual Signatory Institution Worksheet About Local Context".

The CIRB defers responsibility to local institutions to conduct any reviews necessary under HIPAA. The CIRB does accept institutional boilerplate language for HIPAA authorizations if an institution incorporates authorization into the consent document.

The CIRB relies on local institutions to identify potential conflicts of interest and to develop conflict management plans. HMH investigators should submit disclosures as per local COI review process. Investigators must submit conflict management plans for themselves or members of the local research team to the CIRB using the "Annual Principal Investigator Worksheet About Local Context" or the "Study-Specific Worksheet About Local Context".

Investigators wishing to use the NCI CIRB must:

1. Contact the HMH RIO Office to request the materials necessary to register as an investigator with the CIRB.

2. Complete, on an annual basis, the "Annual Principal Investigator Worksheet About Local Context" and submit to the HMH RIO Office and to the CIRB. Once CIRB-approved, the investigator may proceed with individual study applications.

3. In order to open individual protocols/studies under the CIRB, the investigator:

    a. Submits an application to the HMH RIO Office that includes the following:

        1. Study Summary and Key Personnel

        2. CIRB "Study-Specific Worksheet About Local Context"

        3. The protocol/research plan version, investigator brochure(s), and model consent currently approved by the NCI CIRB

        4. The consent form for local use with required local institutional language incorporated

        5. Translations of the consent form for local use with accompanying certificates of translation

        6. Any intended local advertisements or recruitment materials

        7. Conflict of Interest Disclosure Forms for each member of the local research team, and

4. The HMH HRPP Office will review the application, facilitate the COI review process, appropriate training, and departmental sign-offs.

    a. The investigator may then proceed with the application to the CIRB by submitting the CIRB "Study-Specific Worksheet About Local Context". Note: If a member of the research team has a COI Management Plan, this must be submitted to the CIRB.

5. Once approved by the CIRB, a copy of the CIRB approval must be submitted to the HMH RIO Office for upload into the electronic system.

Ongoing responsibilities after study approval:

1. HMH is responsible per written agreement with the CIRB to ensure compliance with the regulations governing research and the determinations made by the CIRB, and to report possible serious or continuing non-compliance and unanticipated problems to the CIRB for evaluation. In order to fulfill these responsibilities HMH needs to maintain current documentation of the study, the actions taken by the CIRB, and any local issues that

arise with the research. On an ongoing basis, the investigator will need to submit the following to the Office of Research Integrity:

a. Amended protocols/research plans, investigator brochure(s), model and local consents, translated consents, local advertisements, recruitment tools, and patient materials, and the associated documentation of CIRB approval;

b. Audit reports;

c. Local unanticipated events, protocol/research plan exceptions, and protocol/research plan deviations;

d. Local subject complaints or unresolved concerns;

e. Changes in local study personnel;

f. Changes in study status locally and study-wide (Open to Enrollment, Closed to Enrollment, Suspended, etc.);

g. Conflict of Interest disclosures on an annual basis or within 30 days of a change in significant financial interests or circumstances that could represent a conflict of commitment;

h. Updated training records (CITI or accepted alternative) for each member of the local research team; and

i. An annual summary of study activity describing the number of local enrollees and status of enrollees (screen failure, on treatment, on follow up, withdrawn, complete, deceased), the study status (open to enrollment, closed to enrollment – active treatment, closed to enrollment – follow up only, closed to enrollment – data analysis, all local activities complete (closed), any shifts in the evidence or in standard care that could impact the target study population or enrollment into the study, and any local complaints, concerns, or problems with the research.

2. The HMH Office of Research Integrity staff will review submissions and seek additional information, if needed, from the local research team. The HMH Office of Research Integrity in consultation with Corporate Compliance will report potential unanticipated problems, potential serious or continuing non-compliance, local suspensions or terminations of research activities, and audit reports that note regulatory deficiencies to the CIRB. The report will include, if applicable, a corrective and preventative action plan (CAPA) developed in cooperation with the investigator. The CIRB will make a final determination regarding whether or not such events are unanticipated problems involving risks to subjects or others, serious non-compliance, or continuing non-compliance and will initiate any necessary reporting to sponsors and federal agencies.

3. Local investigators are responsible for submitting any COI management plans, translated consent forms (with accompanying certificate of translation), local subject materials, and local advertisements and recruitment materials to the CIRB.

4. Research open under the CIRB remains subject to HMH and HRPP policies and procedures including, but not limited to, internal and external audits, training requirements, advertisements, privacy, and confidentiality.

10 Documentation and Records

HMH prepares and maintains adequate documentation of the IRB's activities. All records are 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.

10.1 IRB Records

IRB records include, but are not limited to:

1. Written operating procedures
2. IRB membership rosters
3. Training records documenting that investigators, IRB members, and IRB staff have fulfilled HMH's human subject training requirements
4. IRB correspondence including reports to regulatory agencies
5. IRB Study Records (Study Files) including correspondence with investigator and research team
6. Documentation of exemptions including exemptions related to emergency uses and when limited IRB review is a condition of exemption
7. Convened IRB meeting minutes
8. Documentation of review by another institution's IRB when appropriate.
9. Documentation of cooperative review agreements, e.g., Memoranda of Understanding (MOUs).
    a. For nonexempt research involving human subjects covered by the 2018 revised Common Rule (or exempt research for which limited IRB review takes place as described in Section 5.4) that takes place at an institution in which IRB oversight is conducted by an IRB that is not operated by the institution, the institution and the organization operating the IRB shall document the institution's reliance on the IRB for oversight of the research and the responsibilities that each entity will undertake to ensure compliance with the requirements of this policy (e.g., in a written agreement between the institution and the IRB, by implementation of an institution-wide policy directive providing the allocation of responsibilities between the institution and an IRB that is not affiliated with the institution, or as set forth in a research protocol);
10. Federal Wide Assurances.
11. IRB Registrations.
12. Documentation of complaints and any related findings and/or resolution.

10.2 IRB Study Files

The IRB maintains a separate file for each protocol (including expanded access), HUD, emergency use, or report it receives for review in the IRB electronic system under a unique identification number assigned by the system. As applicable, protocol files include, but are not limited to the following:

1. The initial application and all associated documents and materials;
2. Modification requests and all associated documents and materials;
3. Continuing review/progress reports and all associated documents and materials, including the rationale for conducting continuing review of research that otherwise would not require continuing review;
4. Closure reports and all associated documents and materials;
5. Reports submitted after study or HUD approval including reports of significant new findings, data and safety monitoring reports, protocol violation reports, complaints, noncompliance, and reports of injuries to subjects including reports of potential unanticipated adverse device events and unanticipated problems involving risks to subjects or others;
6. IRB-approved consent, parental permission, and assent forms;
7. DHHS-approved sample consent form and protocol;
8. Grant application;
9. IRB reviewer forms and checklists (when expedited review procedures are used);
10. Documentation of scientific or scholarly review (if available);
11. Documentation of the type of IRB review. For exempt determinations and expedited review, this will include the category under which the review is allowed;
12. For expedited review, documentation of any findings and determinations required by the regulations and study-specific findings supporting those determinations, including, but not limited to, waiver or alteration of consent, waiver of documentation of consent, research involving pregnant women, fetuses, and neonates, research involving prisoners, and research involving children. For research reviewed by the convened board these findings and determinations are recorded in the minutes;
13. For expedited review, documentation of the risk determination and period of approval (when continuing review is required). For research reviewed by the convened board these determinations are recorded in the minutes;
14. For expedited review, the rationale for an expedited reviewer's determination under 45 CFR 46.110(b)(1)(i) that research appearing on the expedited review list described in 45 CFR 46.110(a) is more than minimal risk.
15. Documentation of all IRB review actions;
16. Notification of expiration of IRB approval to the investigator;
17. Notification of suspension or termination of research;

18. Letters to investigator informing them of IRB review outcomes;
19. IRB correspondence to and from investigators related to the protocol;
20. All other IRB correspondence related to the research;
21. For studies evaluating the safety or effectiveness of medical devices, documentation of the device determination (exempt, non-significant risk, significant risk);
22. Reports of unanticipated problems involving risk to subjects or others; and
23. Any statements of significant new findings provided to subjects.

The IRB maintains a separate IRB study file for each research application (study) that it receives for review. Research studies are assigned a unique identification number that begins with the year of review. Accurate records are maintained of all communications to and from the IRB. Copies are kept electronically in the electronic research submission system. HMH IRB maintains a separate electronic file for each research study that includes, but is not limited to:

1. Research plan and all other documents submitted as part of a new study application including:
    - Complete Protocol Application form
    - Proposed Consent / Parental Permission / Assent Form(s) (when applicable)
    - Recruitment materials / subject information (when applicable)
    - Data collection instruments (including all surveys and questionnaires)
    - Investigator Brochure (when one exists)
    - The complete protocol (when one exists)
    - Scientific evaluations, when provided by an entity other than the IRB.
2. Research plan and all other documents submitted as part of a request for continuing review or closure of research application.
3. Documents submitted and reviewed after the study has been approved, including modification requests, protocol/research plan exception requests, proposed advertisements, data and safety monitoring reports, and reports of protocol/research plan violations, complaints, non-compliance, unanticipated adverse device events and unanticipated problems.
4. Copy of IRB-approved Consent/Assent/Permission Forms
5. DHHS-approved sample consent form document and research plan, when they exist
6. Documentation of scientific or scholarly review (if available).
7. Documentation of type of IRB review. For exempt determinations and expedited review, this will include the category under which the review is allowed.

8. For expedited review, documentation of any findings and determinations required by the regulations and study-specific findings supporting those determinations, including, but not limited to, waiver or alteration of consent, waiver of documentation of consent, research involving pregnant women, fetuses, and neonates, research involving prisoners, and research involving children. For research reviewed by the convened board these findings and determinations are recorded in the minutes.
9. For expedited review, documentation of the risk determination and period of approval. For research reviewed by the convened board these determinations are recorded in the minutes.
10. Documentation of all IRB review actions.
11. Notification of expiration of IRB approval to the investigator and requirements related to the expiration.
12. Notification of suspension or termination of research.
13. Copies of approval letters and forms that describe any requirements that the investigator must satisfy before beginning the study.
14. IRB correspondence to and from research investigators.
15. All other IRB correspondence related to the research.
16. For devices, documentation of determination by IRB of significant risk/non-significant risk.
17. Reports of unanticipated problems involving risk to subjects or others.
18. Copies of reports of injuries to participants.
19. Data and safety monitoring reports, if any.
20. Significant new findings.
21. The justification for using the expedited procedure for continuing review of research, if appropriate
22. Documentation of audits, investigations, reports of external site visits.

10.3 The IRB Minutes

Proceedings are written and available for review by the next regularly scheduled IRB meeting. Once accepted by the members, the minutes must not be altered by anyone including a higher organizational authority.

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

Minutes of IRB meetings must contain sufficient detail to show:

1. Attendance
    a. Names of members or alternates present

b. Names of members or alternate members who are participating through videoconference or teleconference and documentation that those attending through videoconferencing or teleconferencing received all pertinent material prior to the meeting and were able to actively and equally participate in all discussions

c. Names of alternates attending in lieu of specified (named) absent members. (Alternates may substitute for specific absent members or categories of members only as designated on the official IRB membership roster)

d. Names of consultants present

e. Names of investigators present

f. Names of guests present

Note: The 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 numbers of members present for the vote on that item. Members who recuse themselves because of conflict of interest are listed by name and the reason documented.

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 and any education provided.
4. Continuing Education
5. Actions taken, including separate deliberations, actions, and votes for each research study undergoing review by the convened IRB.
6. Vote counts on these actions (Total Number Voting; Number voting for; Number voting against; Number abstaining; Number of those recused)
7. Basis or justification for actions disapproving or requiring changes in research
8. Summary of controverted issues and their resolution
9. Approval period for initial and continuing reviews, including identification of research that warrants review more often than annually and the basis for that determination
10. The rationale for requiring continuing review of research that otherwise would not require continuing review as described in Section 7.7;
11. Risk determination for initial and continuing reviews, and modifications when the modification alters the prior risk determination
12. Justification for deletion or substantive modification of information concerning risks or alternative procedures contained in the approved consent document.
13. Study-specific findings supporting that the research meets each of the required criteria when approving a consent procedure that does not include or that alters some or all of

the required elements of informed consent, or when waiving the requirement to obtain informed consent altogether

14. Study-specific findings supporting that the research meets each of the required criteria when the requirements for documentation of consent are waived
15. Study-specific findings supporting that the research meets each of the criteria for approval for vulnerable populations under any applicable Subparts, as well as for research involving participants with diminished capacity.
16. Significant risk/non-significant risk device determinations and the basis for those determinations.
17. Determinations of conflict of interest and acceptance or modification of conflict management plans
18. Identification of any research for which there is need for verification from sources other than the investigator that no material changes are made in the research.
19. Review of interim reports, e.g., unanticipated problems or safety reports; modification requests; report of violation/deviations; serious or continuing non-compliance; suspensions/terminations, etc.
20. A list of research approved under expedited review procedures including limited IRB reviews conducted using expedited procedures since the time of the last such report.
21. An indication that, when an IRB member or alternate has a conflicting interest (see Section 21.2) with the research under review, the IRB member or alternate was not present during the final deliberations or voting.
22. Key information provided by consultants will be documented in the minutes or in a report provided by the consultant.

10.4 IRB Membership Roster

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

1. Name.
2. Earned degrees.
3. Employment or other relationship between each member and the organization (i.e., affiliated or non-affiliated). To be categorized as non-affiliated, neither the member nor an immediate family member of the member may be affiliated with the HMH.
4. Status as scientist or non-scientist. Members whose training, background, and occupation would incline them to view scientific activities from the standpoint of someone within a behavioral or biomedical research discipline are considered a scientist for the purposes of the roster, while members whose training, background, and

occupation would incline them to view research activities from a standpoint outside of any biomedical or behavioral scientific discipline are considered a nonscientist.

5. Indications of experience, such as board certifications, licenses, and areas of practice sufficient to describe each member's chief anticipated contributions to IRB deliberations.
6. Representative capacities of each IRB member; including which IRB member(s) is a prisoner representative, and which IRB members are knowledgeable about or experienced in working with children, pregnant women, cognitively impaired individuals, and other vulnerable populations commonly involved in HMH research.
7. Role on the IRB (Chair, Vice-Chair, etc.)
8. Voting status
9. For alternate members, the primary member or class of members for whom the member could substitute

The IRB office must keep the IRB membership list current. The RIO Manager will report changes in IRB membership to OHRP/FDA within 90 days of the change.

10.5 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 satisfies the conditions of the cited exemption category as detailed in Section 6.

10.6 Documentation of Expedited Reviews

IRB records for initial and continuing review by the expedited procedure must include: the specific permissible category; that the activity described by the investigator satisfies all of the criteria for approval; the approval period and any determinations required by the regulations including study-specific findings justifying the following determinations:

1. Approving a procedure which waives or alters the informed consent process;
2. Approving a procedure which waives the requirement for documentation of consent;
3. Approving research involving pregnant women, human fetuses, or neonates;
4. Approving research involving prisoners;
5. Approving research involving children.

10.7 Access to IRB Records

The IRB has policies and procedures to protect the confidentiality of research information:

1. All IRB records are kept secure in locked filing cabinets or locked storage rooms. Doors to the IRB Offices are closed and locked when the rooms are unattended.

2. Ordinarily, access to all IRB records is limited to the Director of the Human Research Protection Program, IRB Chair, IRB members, RIO Manager, IRB staff, authorized organizational officials, and officials of federal and state regulatory agencies (e.g., OHRP and FDA). Research investigators are provided reasonable access to files related to their research. Appropriate accreditation bodies are provided access. All other access to IRB records is limited to those who have legitimate need for them, as determined by the IO and Director.
3. Records are accessible for inspection and copying by authorized representatives of federal regulatory agencies during regular business hours.
4. Records may not be removed from the IRB Office; however, the IRB staff will provide copies of records for authorized personnel if requested.
5. All other access to IRB study files is prohibited.

10.8 Record Retention

In order to comply with the requirements of OHRP, FDA, and HIPAA, IRB records are maintained at the facility for at least six (6) years after completion of the research.

IRB records for research cancelled without participant enrollment will be retained at the facility for at least 3 years after closure.

After that time those records will be shredded or otherwise destroyed.

11 Obtaining Informed Consent from Research Subjects

No investigator conducting research under the auspices of HMH 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 11.9 of these procedures. Except as provided in Sections 11.10 and 11.11 of these procedures, informed consent must be documented by the use of a written consent form approved by the IRB.

The IRB will evaluate both the consent process and the procedures for documenting informed consent to ensure that adequate informed consent is obtained from participants.

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

11.1 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.

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

11.2 Basic Requirements

Except as provided elsewhere in these Standard Operating Procedures:

1. Before involving a human subject in research, an investigator (or consent delegate per the Delegation of Authority Log (DoA log) shall obtain the legally effective informed consent of the subject or the subject's LAR
2. An investigator shall seek informed consent only under circumstances that provide the prospective subject or the LAR sufficient opportunity to discuss and consider whether to participate and that minimize the possibility of coercion or undue influence
3. The information that is given to the subject or the LAR shall be in language understandable to the subject or the LAR
4. The prospective subject or the LAR must be provided with the information that a reasonable person would want to have to make an informed decision about whether to participate, and an opportunity to discuss that information.
5. Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or LAR in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension
6. Informed consent must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of

isolated facts, but rather facilitates the prospective subject's or LAR's understanding of the reasons why one might or might not want to participate

7. No informed consent may include any exculpatory language through which the subject or the LAR is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

The requirement to obtain the legally effective informed consent of individuals before involving them in research is one of the central protections provided for by the Federal regulations and HMH IRB. Investigators are required to obtain legally effective informed consent from a subject or the subject's Legally Authorized Representative unless the requirement has been waived by the IRB. When informed consent is required, it must be sought prospectively, and properly documented.

The informed consent process involves three key features: (1) disclosing to the prospective human subject information needed to make an informed decision; (2) facilitating the understanding of what has been disclosed; and (3) promoting the voluntariness of the decision about whether or not to participate in the Research.

Informed consent is more than just a signature on a form. It is a process of information exchange to include reading, discussion, receiving answers to any questions, and signing the consent document. The informed consent process is the critical communication link between the prospective Human Subject and an Investigator, beginning with the initial approach of an Investigator and continuing through the completion of the Research study. Investigators must have received the appropriate training and be knowledgeable about the study Protocol in order that they may answer questions to help provide understanding to the study participant or potential study potential study participant. The exchange of information between the Investigator and study participant can occur via one or more of the following modes of communication, among others; face to face dialogue; mail; telephone; or fax; however, obtaining informed consent must allow for a dialogue so that the potential subject has the opportunity to ask questions and receive responses. Investigators must obtain consent prior to entering a subject into a study, gathering data about a subject, and/or conducting any procedures required by the research plan, unless consent is waived by the IRB.

If someone other than the investigator conducts the interview and obtains consent, the investigator needs to formally delegate this responsibility on a Delegation of Authority Log (DoA Log), 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 have the expertise be able to answer questions about the study including those regarding risks, procedures, and alternatives. Determination of this appropriate expertise is determined by the PI.

Sample or draft consent documents may be developed by a sponsor or cooperative study group. However, the IRB-of-record is the final authority on the content of the consent documents that is presented to the prospective study subjects.

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

11.3 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, permission must be obtained from a legal guardian or a legally authorized representative.
2. The informed consent process provides the prospective subject (or legally authorized representative) with sufficient opportunity to read the consent document, when applicable.
3. 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.
4. The informed consent process shall be sought under circumstances that minimize the possibility of coercion or undue influence.
5. 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.
6. For subjects whose native language is not English, informed consent must be obtained in a language that is understandable to the subject (or the subject's legally authorized representative). In accordance with this policy, the IRB requires that informed consent discussions include a reliable interpreter when the prospective subject does not understand the language of the person who is obtaining consent.
7. The informed consent process may not include any exculpatory language through which the subject is made to waive, or appear to waive any of the subject's legal rights or through which the investigator, the sponsor, the Organization or HMH employees or agents are released from liability for negligence, or appear to be so released.
8. The investigator is responsible for ensuring that each prospective subject is adequately informed about all aspects of the research and understands the information provided.

11.4 Determining a potential adult subject's ability to consent to research

For the purpose of this section, a subject has the capacity to consent to his or her own participation in a research activity if s/he demonstrates an appreciation:

1. That the activity is research
2. Of the risks and benefits of a study
3. Of the study procedures and requirements

4. Of the alternatives that are available if not participating
5. That, by choosing not to participate, this decision will be accepted without penalty

In reaching a decision about participation, it is essential for the potential subject to demonstrate an ability to use this information in a rational manner. Thus, in considering risks, benefits, and available alternatives, subjects must show they understand the aspects of these factors that are unique to them as individuals.

See Section 12.8 for further discussion regarding adults who cannot consent for themselves.

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

The investigator and research staff must have adequate procedures in place for assessing and ensuring subjects' capacity, understanding, and informed consent or assent. The IRB will evaluate whether the proposed plan to assess capacity to consent is adequate including consideration of state and local law and organizational policy.

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

Both investigators and IRB members must be aware that for some subjects, their decision-making capacity may fluctuate. For subjects with fluctuating decision-making capacity or those with decreasing capacity to provide consent, periodic reevaluation of capacity and re-consent or consent for continuing participation by a legally authorized representative may be necessary.

In the event that research participants lose or become impaired in decision-making capacity after enrollment, and this is not anticipated in the research plan, the investigator is responsible for notifying the IRB. The investigator is responsible for developing a plan for the IRB's consideration which follows the guidelines outlined above for persons with fluctuating or diminishing capacity.

Whenever the participants have the capacity to give consent (as determined by qualified professionals), informed consent should be obtained and document in accordance with Section 11.6 above. When participants lack the capacity to give consent, investigators may obtain consent from the legally authorized representative of a subject as described in Section 12.8.

When assent is possible for some or all subjects, the investigator should provide the IRB with an assent plan that describes when and how assent will be obtained, provisions that will be taken to promote understanding and voluntariness, and how assent will be documented. Under no circumstances may subjects be forced or coerced to participate.

If the investigator plans to use audio or videotapes, computer video presentations, or written materials, to promote understanding, these materials must be provided to the IRB for review. If the investigator intends to use audio or video recordings to document assent, provisions to ensure the security of the recordings should be described to the IRB. If the investigator will use an assent form to document assent, this must be submitted to the IRB for review.

11.5 Basic Elements of Informed Consent

To be valid, the consent process must provide the following basic elements of information to potential subjects:

1. A statement that the **study involves research**, an explanation of the **purposes** of the research and the **expected duration** of the subject's participation, a description of the **procedures** to be followed, and identification of any **procedures which are experimental**;
2. A description of any reasonably foreseeable **risks** or discomforts to the subject;
3. A description of any **benefits** to the subject or to others which may reasonably be expected from the research;
4. A disclosure of appropriate **alternative procedures** or courses of treatment, if any, that might be advantageous to the subject;
5. A statement describing the extent, if any, to which **confidentiality** of records identifying the subject must be maintained;
6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
7. An explanation of whom to contact 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;
8. 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.
9. 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;
10. One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:

a. A statement that **identifiers might be removed** from the identifiable private information or identifiable biospecimens **and that**, after such removal, the information or biospecimens **could be used** for future research studies or distributed to another investigator for future research studies **without additional informed consent** from the subject or the legally authorized representative, if this might be a possibility; or

b. A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, **will not be used or distributed** for future research studies.

11. For **FDA-regulated studies**, a statement that notes the possibility that the Food and Drug Administration may inspect the records;

12. For "applicable" **FDA-regulated clinical trials,** the following statement must be included verbatim:

    "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

    Applicable clinical trials are (1) clinical trials of drug and biological products that are controlled, clinical investigations other than Phase I investigations, of a product subject to FDA regulation; and (2) prospective clinical studies of health outcomes comparing an intervention with a device product against a control in humans (other than small feasibility studies) or any pediatric post-market surveillance studies required by FDA under the FD&C Act.

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

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
3. Any additional costs to the subject that may result from participation in the research;
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
5. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject;
6. The approximate number of subjects involved in the study.
7. A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;

8. A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions;
9. For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

11.6 Documentation of Informed Consent

Except as provided in Section 11.10 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 using 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. The person obtaining consent will also sign the consent form for greater than minimal risk studies.
2. A copy of the signed and dated consent form must be given to the person signing the form. The investigator should retain the signed original in the research records.
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 investigator shall give either the subject or the subject's LAR adequate opportunity to read the informed consent form before it is signed; alternatively, this form may be read to the subject or the subject's legally authorized representative;

       or

    b. A short form written consent document stating that the elements of informed consent have been presented orally to the subject or the subject's legally authorized representative and that the key information was presented first to the subject, before other information, if any, was provided.

    Short form use is limited to situations when both are true:

    • A full-length version of the consent form in a language understandable to the subject is not available, and

    • It is in the subject's best medical interest to be enrolled in the research before a translated consent form can be obtained.

The subject or their LAR must be reconsented with the current IRB-approved consent form in a language understandable to the subject within 60 (business) days or at the first visit after receipt of the translated consent form (whichever is less).

When this method is used:

i. The oral presentation and the short form written document should be in a language understandable to the subject; and

ii. There must be a witness, who is fluent in both English and the subject's language, to the oral presentation; and
iii. The IRB must approve a written summary of what is to be said to the subject (the approved full consent document may serve as this summary and be read by the interpreter); and
iv. The short form document is signed by the subject;
v. The witness must sign both the short form and a copy of the summary; and
vi. The person obtaining consent must sign a copy of the summary; and
vii. A copy of the summary must be given to the subject or representative, in addition to a copy of the short form.
viii. The original signed English summary and the originally signed short form should be retained in the subject's research record and medical record, if appropriate
ix. The PI will then obtain a fully translated version of the currently approved consent form at the earliest opportunity. The subject would then be reconsented using the translated consent form within 60 (business) days or at the first visit after receipt of the translated consent form (whichever is less).

When this procedure is used with subjects who do not speak, or read, English, or have limited proficiency in oral or written 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. When the person obtaining consent is assisted by an interpreter, the interpreter may serve as the witness.

The IRB must receive all foreign language versions of the short form document as a condition of approval. Expedited review of these versions is acceptable if the protocol/research plan, the full English language informed consent document, and the English version of the short form document have already been approved by the convened IRB.

Language Services:

a) translations of consent forms must be done by a certified translator through Language Services;

b) if the sponsor or cooperative group provide a translated consent, this may be used along with HMH's institutional consent form language translated and provided as an addendum.

11.7 Special Consent Circumstances

11.7.1 Enrollment of persons with limited English-language proficiency

1. **Expected enrollment**: In some studies, the investigator may be able to anticipate enrollment of persons who do not speak or read, or have limited proficiency in, oral or written English. When the target subject population includes such persons or the investigator and/or the IRB otherwise anticipates that consent will be conducted in a language other than English, the IRB requires a translated consent document, and other subject materials, to be prepared. In order to ensure that translated documents are accurate, the IRB may choose to require a certified translation, to have an independent back-translation or to have a review of the translated documents by an IRB member or other person who is fluent in that language. When non-English speaking subjects enroll, they and a witness sign the translated consent document. The consensus approach may be used for documents other than the informed consent document. When the consensus approach is utilized, the IRB shall be provided with the names of the individuals who performed the translation. The **subjects are given a copy of the signed translated consent document.**

2. **Unexpected enrollment:** If a person who does not speak or read, or has limited proficiency in, English presents for possible enrollment, an IRB-approved translated version of the written consent may not be available for use. Investigators should carefully consider the ethical and legal ramifications of enrolling subjects when a language barrier exists. If the subject does not clearly understand the information presented during the consent process or in subsequent discussions, his/her consent may not be informed, and therefore, not effective.

   If an investigator decides to enroll a subject into a study for which there is not an extant IRB-approved consent document in the prospective subject's language, the investigator must receive IRB approval to follow the procedures for a “short form” written consent in as described in Section 11.6.

3. **Use of interpreters in the consent process:** Unless the person obtaining consent is fluent in the prospective subject’s language, an interpreter will be necessary to facilitate the consent discussion. Preferably someone who is independent of the subject (i.e., not a family member) should assist in presenting information and obtaining consent. Whenever possible, interpreters should be provided copies of the translated consent, or short form and the IRB-approved consent script (typically the English-language version of the consent document) well before (24 to 48 hours if possible) the consent discussion with the subject. If the interpreter also serves as the witness, she/he may sign the translated consent, or short form consent document and script, as the witness and should note “Interpreter” under the signature line. The person obtaining consent must document that the “short form” process was used in the subject's research record, including the name of the interpreter.

11.7.2 Braille consent

For blind subjects who read Braille, the IRB may approve a consent document prepared in Braille. In order to assure itself that a Braille consent document is accurate, the IRB may require a transcription into print text or review of the document by an IRB member or other person who reads Braille. If possible, the subject will sign the Braille consent; otherwise oral consent will be obtained, witnessed and documented as described under "Oral Consent" (see Section 11.7.4).

11.7.3 Consenting in American Sign Language (ASL)

For deaf subjects who are fluent in ASL, the IRB may approve a consent process using ASL and the IRB-approved written consent form. When this process is approved, the individual authorized to consent prospective subjects must use a HMH certified interpreter fluent in ASL to conduct the consent process and the documentation of the consent process must conform to the requirements set forth in Section 11.6.

11.7.4 Oral Consent

When subjects are unable to read a written consent form (such as blind or illiterate subjects), the IRB may approve an oral consent process, provided the subject (1) retains the ability to understand the concepts of the study and evaluate the risk and benefit of being in the study when it is explained orally and (2) is able to indicate approval or disapproval to study entry.

For research that is no more than minimal risk, documentation of consent may be waived according to the criteria in Section 11.9.

For greater than minimal risk research, the consent form must be read to the subjects and the subjects must be given an opportunity to ask questions. An audiotape approved by the IRB may also be used. If capable of doing so, the subject signs, or marks an X to signify consent. If that is not possible, the subject will provide oral consent. The person obtaining consent and a witness will sign the written study consent form with a statement that documents that an oral process was used and, if necessary, that the subject gave oral consent. The consent process will also be documented in the subject's research record. Signed copies of the consent form are given to the subject and, whenever possible, these documents should be provided to the subject on audio or videotape.

11.8 Subject Withdrawal or Termination

For a variety of reasons, a subject enrolled in a research study may decide to withdraw from the research, or an investigator may decide to terminate a subject's participation in research regardless of whether the subject wishes to continue participating. Investigators must plan for the possibility that subjects will withdraw from research and include a discussion of what withdrawal will mean and how it will be handled in their research protocols/research plans and consent documents.

When seeking informed consent from subjects, the following information regarding data retention and use must be included:

- For FDA-regulated clinical trials, when a subject withdraws from a study, the data collected on the subject to the point of withdrawal remain part of the study database and may not be removed. The consent document cannot give the subject the option of having data removed.
- For research not subject to FDA regulations, the investigator should inform subjects that they can allow the investigator to retain and analyze already collected data relating to the subject up to the time of subject withdrawal; or request that the investigator destroy the subject's data.

When a subject's withdrawal request is limited to discontinuation of the primary interventional component of a research study, research activities involving other types of participation for which the subject previously gave consent may continue. Investigators should ask a subject who is withdrawing whether the subject 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 subject would distinguish between study-related interventions and procedures and continued follow-up in person, by phone, or via records review, of data and address the maintenance of privacy and confidentiality of the subject's information.

If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up as described in the previous paragraph, the investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original consent document). IRB approval of consent documents for these purposes would be required.

If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up, the investigator must not access or gather private information about the subject for purposes related to the study. However, an investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.

11.9 Waiver of Informed Consent

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

1. The research or clinical investigation involves no more than minimal risk to the subjects;
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
3. The research or clinical investigation 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.

General Waiver or Alteration:
An IRB may waive the requirement to obtain informed consent, provided the IRB finds and documents that the below criteria are satisfied. An IRB **may not** waive or alter broad consent, nor may it waive consent for the storage, maintenance, or secondary research use of identifiable biospecimens if an individual was asked to provide broad consent and refused.
Likewise, an IRB may approve a consent procedure that omits some, or alters some or all, of the basic and additional elements of informed consent (an "alteration"), provided that the IRB finds and documents that the below criteria are satisfied. An IRB **may not** omit or alter any of the general requirements for informed consent. If a broad consent procedure is used, an IRB **may not** omit or alter any of the required elements of broad consent.

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

This option applies to both FDA-regulated and DHHS-conducted or supported research.
In addition, an IRB may approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent; or waive the requirements to obtain informed consent, provided the IRB finds and documents that:

1. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
    a. Public benefit or service programs;
    b. Procedures for obtaining benefits or services under those programs;
    c. Possible changes in or alternatives to those programs or procedures; or
    d. Possible changes in methods or levels of payment for benefits or services under those programs; and,
2. The research could not practicably be carried out without the waiver or alteration.

Public Benefit or Service Programs Waiver or Alterations

An IRB may waive the requirement to obtain informed consent, provided the IRB finds and documents that the below criteria are satisfied. An IRB **may not** waive or alter broad consent, nor may it waive consent for the storage, maintenance, or secondary research use of identifiable biospecimens if an individual was asked to provide broad consent and refused.

Likewise, an IRB may approve a consent procedure that omits some, or alters some or all, of the basic and additional elements of informed consent (an "alteration"), provided that the IRB finds and documents that the below criteria are satisfied. An IRB **may not** omit or alter any of the general requirements for informed consent. If a broad consent procedure is used, an IRB **may not** omit or alter any of the required elements of broad consent.

1. The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:
    a. Public benefit or service programs;
    b. Procedures for obtaining benefits or services under those programs;
    c. Possible changes in or alternatives to those programs or procedures; or
    d. Possible changes in methods or levels of payment for benefits or services under those programs; and
2. The research could not practicably be carried out without the waiver or alteration.

This option **does not** apply to FDA-regulated research.

11.10 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 if it finds any of the following:

1. The only record linking the subject and the research would be the informed consent form and the principal risk would be potential harm from a breach of confidentiality (e.g., domestic violence research where the primary risk is discovery by the abuser). Each subject (or LAR) will be asked whether they want documentation linking them with the research, and their wishes must govern.

    This option **does not** apply to FDA-regulated research.
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-investigators (e.g., marketing surveys, telemarketing).

    This option **does** apply to FDA-regulated research (most commonly in the context of minimal risk screening activities that are necessary to determine eligibility for enrollment in a clinical trial).
3. If the subjects or LARs are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

    This option **does not** apply to FDA-regulated research.

Unless the IRB has granted a full waiver of the requirement to obtain informed consent, investigators who seek and receive approval for a waiver of documentation of consent still must perform an appropriate consent process.
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.

11.11 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 DHHS at 61 FR 51531-33 for non-FDA-regulated 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 who are in need of emergency medical intervention, cannot provide legally effective informed consent themselves, and there is generally insufficient time and opportunity to locate and obtain consent from their legally authorized representatives (LARs).

The Secretary of Health and Human Services (DHHS) has implemented an Emergency Research Consent Waiver under *45 CFR 46.101(i)* with provisions equivalent to those of the FDA with the exception of the requirements specified in Sections 11.11.2.1 and 11.11.2.2 below. The DHHS waiver is not applicable to research involving prisoners, pregnant women, fetuses, or in vitro fertilization.

11.11.1 Definitions

Planned Emergency Research. It is research that involves subjects who, are in a life-threatening situation for which available therapies or diagnostics are unproven or unsatisfactory, and because of the subjects' medical condition and the unavailability of legally authorized representatives of the subjects, it is generally not possible to obtain legally effective informed consent.

Family Member. For this section means any one of the following adult and legally competent persons: spouses; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship.

11.11.2 Procedures

The IRB may approve the planned emergency research without requiring informed consent of all research subjects prior to initiating the research intervention if the IRB finds and documents that the following conditions 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 research.

(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 research 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 research could not practicably be carried out without the waiver.

(5) The proposed research 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 Sections 46.116 and 46.117 of 45 CFR 46 and Sections 50.20, 50.25 and 50.27 of 21 CFR 50. 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 research consistent with paragraph (7)(v) of this section.

(7) 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 research will be conducted and from which the subjects will be drawn;

(ii) Public disclosure to the communities in which the research 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 research to apprise the community and investigators 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 research; 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 research. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

In addition, 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 research, the details of the research 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 research and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into research with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the research is to be provided to the subject's legally authorized representative or family member, if feasible.

11.11.2.1 FDA-regulated Planned Emergency Research

1) A licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation must concur that the conditions described in Section 11.11.2 are satisfied.

2) Studies 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 that such studies may include subjects who are unable to consent. The submission of those studies 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.

3) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided in the regulations 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.

4) The IRB determinations and documentation required in Section 11.11.2 and paragraph 3 above 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).

11.11.2.2 Planned Emergency Research Not Subject to FDA Regulations

1) The IRB responsible for the review, approval, and continuing review of the research has approved both the research and a waiver of informed consent and has (i) found and documented that the research *is not subject* to regulations codified by the FDA at 21 CFR Part 50, and (ii) found and documented **and** reported to the OHRP that the conditions required Section 11.11.2 have been met relative to the research.

11.12 Consent Via Electronic Communication

Consent via Electronic Communication (Electronic Consent) means obtaining consent via electronic communication, either by telephone or real-time audio/video such as ZOOM, and recording a secure electronic signature as described in this section. Electronic consenting is permitted and encouraged, when appropriate.

Hackensack Meridian *Health* currently holds an institutional contract with DocuSign, a company that provides for secure electronic consenting (https://www.docusign.com/products/electronic-signature). Instructions on DocuSign use can be found at the following link: https://support.docusign.com/en/guides/dses-user-guide. Other methods for obtaining electronic consent, such as the use of REDCap, may be permitted, if they are HIPAA compliant. If researchers are unsure of whether a particular platform is appropriate for electronic consenting in a research setting, they are encouraged to reach out to the Research Integrity Office.

The electronic consenting forms and processes should conform to standard consenting guidelines. The only difference should be that it is not in person. Thus, the consent process,

including an explanation of the study and full review of the consent form, must precede the participant's signature on the document. The researcher should send the consent form to the participant and should arrange a call to review it together. Once the researcher has explained the study and the potential participant has had the opportunity to ask questions, then the potential participant may sign the consent electronically and send it back to the researcher.

A witness is required in cases of non-English speaking participants who are utilizing a translator and with some vulnerable populations, including when a legally authorized representative (LAR) is being utilized. These are the same situations in which the regulations would normally require one; a witness is not required simply because electronic consent is being implemented in lieu of face-to-face consent. The witness should be present throughout the phone call with the participant; however, s/he may not be able to witness the actual signature, just the conversation preceding the signature.

In general, the participant's and researcher's signatures should have matching dates on them. However, if there is a slight delay because of the electronic nature of the consent, dates that are a day apart may be allowed. It is necessary for the researcher to provide an explanation as a Note to File in those circumstances.

12 Vulnerable Subjects in Research

When some or all of the participants in research conducted under the auspices of HMH are likely to be vulnerable to coercion or undue influence or have diminished decision-making capacity, the research must include additional safeguards to protect the rights and welfare of these participants. The IRB must ensure that all of the regulatory requirements for the protection of vulnerable subjects are met and that appropriate additional protections for vulnerable subjects are in place.

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

12.1 Definitions

Children. Children are 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.

According to New Jersey State Law, minors are persons under the age of eighteen. The general rule is that a person may consent for his or her own medical care at the age of eighteen. Therefore, HMH IRB defines children as persons who are under eighteen years of age. Certain statutes and case law, however, provide minors with "majority" status in some circumstances, giving them the right to consent to their own medical care. For example: emancipated minors New Jersey law enumerates certain categories of individuals who, although under the age of 18, have the right to make medical decisions on their own behalf, such as minors who are

married, widowed or divorced, minors who are parents, etc.); mature minors New Jersey law recognizes that some minors may be sufficiently "mature" to give consent to medical treatment, even though they do not qualify as "emancipated"); or certain minors seeking care for drug addiction, sexually transmitted diseases, emotional disorders, or abortion or mental health treatment. Because New Jersey law does not specifically address consent of children with majority status to research, HMH IRB will review issues of consent related to enrollment of these children in research on a case-by-case basis.

NOTE: For research conducted in jurisdictions other than New Jersey, the research must comply with the laws regarding the legal age of consent in the relevant jurisdictions. HMH's Legal counsel will be consulted with regard to the laws in other jurisdictions.

Guardian. A guardian is an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care.

In New Jersey a "Guardian" of a child means a court-appointed person with the duty and authority to act in the best interests of the minor, subject to residual parental rights and responsibilities, to make important decisions in matters having a permanent effect on the life and development of the minor and to be concerned with his or her general welfare. [NJ 4:86]

NOTE: For research conducted in jurisdictions other than New Jersey, the research must comply with the laws regarding guardianship in all relevant jurisdictions. HMH's Legal counsel will be consulted with regard to the laws in other jurisdictions.

Fetus. A fetus means the product of conception from implantation until delivery.

Dead fetus. A fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.

Delivery. A delivery is a complete separation of the fetus from the woman by expulsion or extraction or any other means.

Neonate. A neonate is a newborn.

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

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

Pregnancy. A pregnancy encompasses 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.

Prisoner. A 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.

12.2 Involvement of Vulnerable Populations

If the IRB reviews research that involves categories of participants vulnerable to coercion or undue influence, the review process should include one or more individuals who are knowledgeable about or experienced in working with these participants. The IRB may include one or more individuals who are knowledgeable about or experienced in working with individuals from these populations or it may seek such expertise through the use of consultants.

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-conducted or supported 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.

In its FWA, HMH limits its commitment to apply Subparts B, C, and D to non-exempt human subjects research conducted or supported by DHHS or any other federal agency that requires compliance with the Subpart(s) (B, C, or D) applicable to the research.

The following policies and procedures, which are based on Subparts B, C, and D, apply to all research regardless of funding. The individual sections describe how the subparts apply specifically to DHHS-funded research.

12.3 Responsibilities

1. The investigator is responsible for identifying the potential for enrolling vulnerable subjects in the research proposal, including the possible inclusion of subjects who are at risk for impaired decisional capacity, and who are being asked to participate in a research study with greater than minimal risk.
2. The IRB shall include representation, either as members or through the use of consultants, of individual(s) who are knowledgeable about or experienced working with the vulnerable populations involved in the research proposal under review.
3. The IRB reviews the investigator's justifications for including vulnerable populations in the research to assess appropriateness for inclusion in the research proposal.
4. The IRB must ensure that appropriate additional safeguards have been included in each study to protect the rights and welfare of vulnerable subjects at the time of initial review of the research proposal.

12.4 Procedures

Initial Review of Research Proposal:

1. The investigator identifies the potential to enroll vulnerable subjects in the proposed research at initial review and provides the justification for their inclusion in the study.
2. The investigator describes safeguards to protect the subject's rights and welfare in the research proposal.
3. The IRB evaluates the proposed safeguards, including, if applicable, the proposed plan for obtaining consent from legally authorized representatives and the plans for assent of children and adults unable to provide consent.
4. The IRB evaluates the research to determine the need for additional protections and considers, if appropriate, the use of a data and safety monitoring board, consent monitor, or research subject advocate.

Continuing Review and Monitoring. At Continuing Review the investigator should identify the number and categories of vulnerable subjects enrolled and any problems that arose relevant to their rights and welfare.

12.5 Research Involving Pregnant Women, Human Fetuses and Neonates

The following applies to all research regardless of funding source. According to the HMH FWA, Subpart B of 45 CFR 46 applies only to DHHS-funded research, the funding-source specific requirements are noted in the appropriate sections.

12.5.1 Research Involving Pregnant Women or Fetuses

12.5.1.1 Research Not Conducted or Supported by DHHS

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

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

1. Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus;
3. Any risk is the least possible for achieving the objectives of the research;
4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, then the

consent of the pregnant woman is obtained in accord with the provisions for informed consent;

5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
6. Each individual providing consent under paragraph 4 or 5 of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children (as defined in Section 12.1) who are pregnant, assent and permission are obtained in accord with the requirements of state law and the IRB;
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
10. Confirmation of the determination regarding viability will be sought from a qualified individual who is not otherwise engaged in the research whenever possible prior to beginning the research. The opinion of the independent qualified individual will be documented and made available upon request to the IRB or HRPP representative. When advance confirmation is not possible, the investigator will obtain it as soon as s/he can after enrollment, but in all cases within 3 business days. The circumstances that prohibited prospective confirmation of viability and the outcome of the subsequent consultation will be reported to the IRB within 5 business days.

12.5.1.2 Research Conducted or Supported by DHHS

For DHHS-conducted or supported research, 45 CFR Subpart B applies to all non-exempt human subject research involving pregnant women, fetuses, and neonates.

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

1. Where scientifically appropriate, pre-clinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
3. Any risk is the least possible for achieving the objectives of the research;

4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, then the consent of the pregnant woman is obtained in accord with the provisions for informed consent.
5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the provisions for informed consent, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
6. Each individual providing consent under paragraph 4 or 5 of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children (as defined in Section 12.1) who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent in Section 12.7.2;
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and
10. Individuals engaged in the research will have no part in determining the viability of a neonate.

12.5.2 Research involving Neonates of Uncertain Viability or Nonviable Neonates

12.5.2.1 Research Not Conducted or Supported by DHHS

Neonates of uncertain viability and nonviable neonates may be involved in research **involving more than minimal risk** 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. The IRB may allow individuals whose normal responsibilities include determining the viability of neonates to be engaged in the research, if their involvement in the determination of viability for an individual neonate cannot be avoided. In such cases, confirmation of the determination regarding viability must be made by a qualified individual who is not otherwise engaged in the research whenever possible prior to beginning the research. The opinion of the independent qualified individual will be documented and made available upon request to the IRB or HRPP representative. When advance confirmation is not possible, the investigator will obtain it as soon as s/he can after enrollment, but in all cases within 3 business days. The circumstances that

prohibited prospective confirmation of viability and the outcome of the subsequent consultation will be reported to the IRB within 5 business days.

4. The requirements of Neonates of Uncertain Viability or Nonviable Neonates (see below in this section) have been met as applicable.

Neonates of Uncertain Viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research 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 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.

Nonviable Neonates. After delivery, nonviable neonates may not be involved in research 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 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.

   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 <u>will not</u> suffice to meet the requirements of this paragraph.

12.5.2.2 Research Conducted or Supported by DHHS

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.

Neonates of Uncertain Viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research 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.

Nonviable Neonates. After delivery, nonviable neonates may not be involved in research 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.

However, if either parent is unable to consent because of unavailability or 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.

12.5.3 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 for Research Involving Children (i.e., a viable neonate is a child for purposes of applying federal regulations and HMH policies).

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

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.

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 these policies and procedures are applicable.

12.5.5 Research Not Otherwise Approvable

12.5.5.1 Research Not Conducted or Supported by DHHS

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

1. That the research in fact satisfies the conditions detailed above, 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.

12.5.5.2 Research Conducted or Supported by DHHS

DHHS conducted or supported research that falls in this category must be approved by the Secretary of Health and Human Services. 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 research will be sent to OHRP for DHHS review.

12.6 Research Involving Prisoners

The following applies to all research involving prisoners, regardless of funding source. The requirements in this section are consistent with Subpart C of 45 CFR 46, which applies to DHHS-funded or supported research.

12.6.1 Applicability

This policy applies to all biomedical and behavioral research conducted under the auspices of HMH involving prisoners as subjects. Even though the IRB may approve a research study involving prisoners as subjects according to this policy, investigators are still subject to the Administrative Regulations of the New Jersey Department of Corrections and any other applicable State or local law. [45 CFR 46.301]

12.6.2 Incarceration of Enrolled Subjects

If a participant becomes a prisoner while enrolled in a research study that was not reviewed according to Subpart C, the investigator must promptly notify the IRB and the IRB shall:

1. Confirm that the participant meets the definition of a prisoner.
1. Consult with the investigator to determine if it is in the best interests of the participant to continue participation in the study, in part or in full, and if so, if there are specific study activities which are in the best interests of the subject and should continue until the IRB is able to review the research study under Subpart C.
2. If the participant should continue, one of two options are available:
    a. Keep the participant enrolled in the study and review the research under Subpart C. If some of the requirements of Subpart C cannot be met or are not applicable (e.g., procedures for the selection of subjects within the prison), but it is in the best interests of the participant to remain in the study, keep the participant enrolled and inform OHRP of the decision along with the justification.
    b. Remove the participant from the study and keep the participant on the study intervention under an alternate mechanism such as compassionate use, off label use, etc.
3. If a participant is incarcerated temporarily while enrolled in a study:

a. If the temporary incarceration has no effect on the study (i.e., there is no need for study activities to take place during the temporary incarceration), keep the participant enrolled.

b. If the temporary incarceration has an effect on the study, follow the above guidance.

12.6.3 Additional Duties of the IRB

In addition to all other responsibilities prescribed for IRB in other sections of this manual, the IRB will review research involving prisoners and approve such research only if it finds that:

- The research falls into one of the following **permitted categories** [45 CFR 46.306(a)(2)]:
  - 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;
  - 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;
  - Research on conditions particularly affecting prisoners as a class (for example, research on diseases or social and psychological problems much more prevalent in prisons) provided that the study may proceed only after the DHHS Secretary has consulted with appropriate experts in penology, medicine, and ethics, and published notice in the Federal Register of his/her intent to approve the research;
  - 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/research plans approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the DHHS Secretary has consulted with appropriate experts in penology, medicine, and ethics, and published notice in the Federal Register of his/her intent to approve the research
- Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;
- The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;
- Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the

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;

- The information is presented in language which is understandable to the subject population;
- Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and
- 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.

12.6.4 Certification to DHHS

Under 45 CFR 46.305(c), the institution responsible for conducting research involving prisoners that is conducted or supported by DHHS shall certify to the Secretary (through OHRP) that the IRB has made the seven findings required under 45 CFR 46.305(a) and receive OHRP authorization prior to initiating any research involving prisoners. Certifications, and requests for DHHS Secretarial consultation, do not need to be submitted to OHRP for research not conducted or supported by DHHS, regardless of whether the institution has chosen to extend the applicability of its FWA and Subparts B, C, and D to all research.

For all DHHS conducted or supported research, HMH 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 study in question and any relevant DHHS grant application or protocol/research plan. DHHS conducted or supported research involving prisoners as subjects may not proceed until OHRP issues its authorization in writing to HMH on behalf of the Secretary under 45 CFR 46.306(a)(2).

Under its authority at 45 CFR 46.115(b), OHRP requires that the institution responsible for the conduct of the proposed research also submit to OHRP 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/research plan; any relevant DHHS grant application or proposal;
- Any IRB application forms required by the IRB;
- And any other information requested or required by the IRB to be considered during initial IRB review.

OHRP also encourages the organization to include the following information in its prisoner research certification letter to facilitate processing:

- The OHRP Federalwide Assurance (FWA) number;
- The IRB registration number for the designated IRB; and
- The date(s) of IRB meeting(s) in which the study was considered, including a brief chronology that encompasses:
  - The date of initial IRB review; and
  - The date of subpart C review, if not done at the time of initial IRB review.

12.6.5 Waiver for Epidemiology Research

The DHHS Secretarial waiver for certain epidemiological research conducted or supported by DHHS functions as a fifth category of permissible research [68 FR 36929]. The criteria for this category are that the research must have as its sole purpose (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. The organization still must review the research under subpart C and certify to OHRP that an appropriately constituted IRB has reviewed the proposal and made all other required findings under DHHS regulations at 45 CFR 46.305(a) and receive OHRP authorization prior to initiating any research involving prisoners. All of the other requirements of subpart C apply to research in this category.

12.7 Research Involving Children

The following applies to all research involving children, regardless of funding source. The requirements in this section are consistent with Subpart D of 45 CFR 46, which applies to DHHS-funded research and Subpart D of 21 CFR 50, which applies to FDA-regulated research involving children.

12.7.1 Allowable Categories

In addition to the IRB's normal duties, research involving children must be reviewed by the IRB to determine if it fits within and is permissible under one or more federally-defined categories (OHRP/FDA). Each procedure or intervention that the child will undergo for the research must be taken into consideration, and, if the research includes more than one study group assignment (e.g., placebo vs. active, investigational agent vs. comparator) the category determination must be made for each group assignment. In other words, a component analysis must be conducted by the IRB. The categories are as follows:

1. **[45 CFR 46.404/21 CFR 50.51] Research/Clinical Investigations not involving greater than minimal risk**. Research determined to not involve greater than minimal risk to child subjects may be approved by the IRB only if the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in Section 12.7.2.

2. **[45 CFR 46.405/21 CFR 50.52] Research/Clinical Investigations involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.** Research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, may be approved by the IRB only if the IRB finds and documents that:

   - The risk is justified by the anticipated benefit to the subjects;
   - The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative options; and
   - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 12.7.2**.**

3. **[45 CFR 46.406/21 CFR 50.53] Research/Clinical Investigations involving greater than minimal risk and no prospect of direct benefit to the individual subject, but likely to yield generalizable knowledge about the subject's disorder or condition.** Research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, may be approved by the IRB only if the IRB finds and documents that:

   - The risk represents a minor increase over minimal risk;
   - The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
   - The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
   - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 12.7.2.

4. **[45 CFR 46.407/21 CFR 50.54] Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children.** When the IRB does not believe that the research meets the requirements of any of the above categories, and the IRB finds and documents 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, the IRB shall refer the research for further review as follows:

   - HHS conducted or supported research in this category will be referred for review by the Secretary of Health and Human Services. However, before doing so the IRB must

determine that the proposed research also meets all of the requirements of the Common Rule.

- FDA-regulated research in this category will be referred for review by the Commissioner of Food and Drugs.
- For research that is not DHHS conducted or supported and not FDA-regulated, the IRB will consult with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law). Based on the recommendation of the panel, the IRB may approve the research based on either:
    - That the research in fact satisfies the conditions of the previous categories, as applicable; or
    - The following:
        - The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
        - The research will be conducted in accord with sound ethical principles; and
        - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 12.7.2.

12.7.2 Parental Permission and Assent

12.7.2.1 Parental Permission

The IRB must determine that adequate provisions have been made for soliciting the permission of each child's parent or guardian.

Parents or guardians must be provided with the basic elements of consent and any additional elements the IRB deems necessary, as described in Section 11.5.

The IRB may find that the permission of one parent is sufficient for research to be conducted under Categories 1 [45 CFR 46.404/21 CFR 50.51] & 2 [45 CFR 46.405/21 CFR 50.52] above. The IRB's determination of whether permission must be obtained from one or both parents will be documented in the reviewer's notes when a study receives expedited review, and in meeting minutes when reviewed by the convened committee.

Permission from both parents is required for research to be conducted under Categories 3 [45 CFR 46.406/21 CFR 50.53] & 4 [45 CFR 46.407/21 CFR 50.54] above unless

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

For research not covered by the FDA regulation, the IRB may waive the requirement for obtaining permission from a parent or legal guardian if:

- The research meets the provisions for waiver in Section 11.9 or
- If the IRB determines that the research 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) provided that an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and that the waiver is not inconsistent with Federal, State, or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol/research plan, the risk and anticipated benefit to the research subjects, and the child's age, maturity, status, and condition.

Parental permission may not be waived for research covered by the FDA regulations.

Permission from parents or legal guardians must be documented in accordance with and to the extent required by Section 11.6.

12.7.2.2 Assent from Children

The IRB is responsible for determining that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. This judgment may be made for all children to be involved in the study, or for each child, as the IRB deems appropriate.

If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accordance with the applicable regulations. It is important to note that the FDA regulations do permit the IRB to waive the assent requirement if it finds and documents that:

1. The clinical investigation involves no more than minimal risk to the subjects;
2. The waiver will not adversely affect the rights and welfare of the subjects;
3. The clinical investigation could not practicably be carried out without the waiver; and
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Because "assent" means a child's affirmative agreement to participate in research, 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.

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.

Parents and children will not always agree on whether the child should participate in research. Where the IRB has indicated that the assent of the child is required in order for him or her to be enrolled in the study, dissent from the child overrides permission from a parent. Similarly, a child typically cannot decide to be in research over the objections of a parent. There are individual exceptions to these guidelines but in general, children should not be forced to be research subjects, even when permission has been given by their parents.

Documentation of Assent

When the IRB determines that assent is required, it also is responsible for determining whether and how assent must be documented. When the research targets the very young child or children unable or with limited capacity to read or write, an oral presentation accompanied perhaps by some pictures with documentation of assent by the person obtaining assent in a research note is likely more appropriate than providing the child a form to sign. In this case, the investigator should provide the IRB with a proposed script and any materials that they intend to use in explaining the research.

When the research targets children who are likely able to read and write, investigators should propose a process and 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.

More than one method for obtaining assent may be used when participants represent a range of ages. For young children who are capable of understanding what is being asked of them but

who cannot yet read, verbal assent may be appropriate. Children between 7 and 13 years of age should be asked to sign an assent form written at the second or third grade reading level. Children 14 and older may be capable of understanding the consent form/parental permission form and can indicate written assent by signing the form as the research participant. The parent cosigns the same form.

Whenever possible, the document should be limited to one page. Illustrations might be helpful, and larger type and other age appropriate improvements are encouraged when they have the potential to enhance comprehension. Studies involving older children or adolescents should include more information and may use more complex language.

12.7.2.3 Children Who are Wards

Children who are wards of the State or any other agency, institution, or entity can be included in research approved under 45 CFR 46.406/21 CFR 50.53 or 45 CFR 46.407/21 CFR 50.54 (Categories 3 & 4 in Section 12.7.1), **only if such research** is:

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

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

The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

12.8 Adults with Impaired Decision Making Capacity

The requirements in this section apply to all research involving adults who cannot provide consent or with impaired decision-making capacity regardless of funding source.

Research involving subjects without the ability to provide consent or with impaired decision-making capacity should only be conducted when the aims of the research cannot reasonably be achieved without their participation. Participation of such subjects in research cannot be justified solely on their availability or the convenience for the investigator.

When an investigator seeks to include such subjects in research, they must disclose this to the IRB and provide justification for why inclusion is necessary. If capacity to consent is questionable, or may fluctuate, investigators should include provisions for determining capacity to provide informed consent (See Section 11.4), and, if appropriate to reevaluate capacity during participation. When capacity to consent may diminish, the procedures should include, when possible and appropriate, designation of a legally-authorized authorized representative (LAR), inclusion of the future LAR in the initial consent discussion and process, and

memorialization of the participant's wishes regarding the research in writing. When the research includes subjects likely to regain capacity to consent, the investigator should include provisions to inform the subject regarding their participation and to seek consent for ongoing participation, if applicable.

When the IRB reviews research involving greater than minimal risk and the proposed subject population includes adults who cannot provide consent, may have impaired capacity to provide consent, or whose capacity can be expected to fluctuate over time, the IRB review process will include at least one member, or a consultant, who is experienced with or otherwise knowledgeable about the population.

New Jersey has separate requirements regarding the Inclusion of Decisionally Impaired Subjects under New Jersey statute 26:14-2. The plan for including decisionally impaired subjects must be submitted to the IRB with the application.

Substituted/Surrogate Consent Under the New Jersey Access to Medical Research Act (N.J.S.A. 26:14-1)

Except for research which is performed pursuant to 21 CFR 50.24, New Jersey law allows for substituted consent for adult subjects with cognitive impairments or other lack of capacity only if:

> (1) The research offers the prospect of direct benefit to the individual subject, and the IRB determines that the risk is justified by the anticipated benefits to the subject and that the relation of the anticipated benefit to the risk is at least as favorable to the subject as that presented by available alternative approaches. In research fitting this description, the person providing substituted consent shall be presented with the choice of the recognized treatment and the research protocol, or:
>
> (2) The research does not offer the prospect of direct benefit to the individual subject, but the IRB has determined that: first, the research is likely to yield generalizable knowledge about the subject's disorder or condition; second, by its very nature the research cannot be conducted without the participation of decisionally incapacitated persons as subjects; third, the research involves no more than a minor increase over minimal risk. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are no greater than those encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Under New Jersey law, all adult subjects are presumed to have the ability to consent unless the subject is unable to voluntarily understand and appreciate the nature of the proposed intervention, the subject's diagnosis and prognosis, the burdens, the benefits and risks of, and the alternatives to any such research and to reach an informed decision.

Process:

A. **Determination of Incapacity:** When research is involved, before a subject can be enrolled based on substituted consent, an attending physician who has no connection to the

study must determine, to a reasonable degree of medical certainty, that the patient lacks the capacity to give informed consent, the extent of that incapacity, and that the patient will not regain decision-making capacity within the time frame for enrolling the subject in the study.

a. **Documentation of Incapacity:** The attending physician's clinical findings and determination must be documented in an IRB-approved statement signed by the attending physician (such as within the signature block of the consent form), and must be placed within the regulatory binder for each subject; a copy of this determination must be provided to the subject and the subject's legally authorized representative. A copy should also be placed in the medical record and the study files.

B. **Legally Authorized Representative - NJ Order of Priority**: Once a determination has been made that a patient lacks capacity to consent, the following persons, in descending order of priority, can give substituted consent on behalf of the subject:

1. the guardian of the subject who has the authority to make health care decisions for the subject;
2. the subject's health care representative named in the subject's advance directive for health care;
3. the subject's spouse or civil union partner, as applicable;
4. the subject's statutory domestic partner [see Section 3 of P.L.2003, 2c.246(C.26:8A-3)];
5. an adult son or daughter;
6. a custodial parent of the subject;
7. an adult brother or sister;
8. an adult grandchild;
9. an available adult relative with the closest degree of kinship to the subject.

Notwithstanding the subjects' incapacity and the availability of a person who could give substituted consent, substituted consent is **not permitted** if:

1. The subject has expressed any dissent or objection to the proposed research, or;
2. In the event there are two or more available persons in the same order of priority who could give substituted consent, and one of those persons has expressed dissent over the subject's participation in the research;
3. If two or more available persons who are in different order of priority who could give substituted consent and a representative of higher authority refuses to consent and a representative of lower authority would give consent.

The following conditions apply when substituted consent is given:

1. Decisions must be made in accordance with the subject's health care instructions or wishes or in accordance with the LAR's best estimation of what the subject would have chosen if the subject were capable.
2. The LAR must not be paid for providing consent.

3. If the subject previously executed an advanced directive and participation in the research would conflict with the provisions of the advanced directive, then the subject must not be included in the research.
4. The investigator must confirm that these requirements are met.

C. Witness of Consent Process: If the IRB has approved the research to include the use of an LAR for consent on behalf of the subject (substituted consent), a person who is not the subject, guardian, authorized representative, or the researcher (principal investigator or Sub-investigator) must attest that the requirements for informed consent to the research have been satisfied and must also sign the consent form.

In evaluating research, the IRB must be able to determine that the risks to subjects are reasonable not only in relation to any benefits, but also in relation to the importance of the knowledge that may reasonably be expected to result. In considering the risks of research involving subjects unable to provide informed consent or with diminished capacity to do so, the IRB should consider whether any components of the research involve risks that are greater for participants with diminished capacity. For example, the population might experience increased sensitivity or discomfort to certain stimuli or may not be able to verbalize or otherwise demonstrate when they are experiencing discomfort or pain.

As appropriate to the research, the IRB will consider the following in evaluating greater than minimal risk research involving adults unable to consent or with impaired decision-making capacity:

1. Whether the aims of the research cannot reasonably be achieved without inclusion of the population
2. Whether the research is likely to improve the understanding of the condition, disease, or issue affecting the subject population
3. Whether any experimental procedure or interventions have undergone pre-clinical testing or human testing on other populations and whether the data from that testing supports its use in the proposed research
4. Whether the procedures or interventions that the subject will undergo in the research place them at increased risk and if appropriate mechanisms are in place to minimize risks, when possible
5. Whether the data and safety monitoring plan, including any stopping rules, is appropriate given the risks of the research and the vulnerability of the population
6. Whether the procedures for withdrawing individual subjects from the research are appropriate
7. Whether the recruitment procedures, consent process, and any plans for financial compensation support voluntariness and minimize the likelihood of undue influence or coercion

8. Whether the subjects will be exposed to financial or other risks that they might not consider acceptable if they had the capacity to provide consent, and whether appropriate mechanisms have been put into place to minimize these risks
9. Whether the procedures for determining capacity to provide consent, and for evaluating capacity on an ongoing basis, if applicable, are appropriate
10. Whether the procedures for informing subjects who regain capacity about their involvement in the research, and for obtaining consent for on-going participation, if applicable, are appropriate
11. Whether assent should be required when possible, and, if so, if the proposed procedures to obtain and document assent are appropriate
12. Whether a research subject advocate or consent monitor should be required, for some or all subjects
13. A written consent document (or other information relevant to the research) will be provided to the research participant and their LAR accompanied by a consent conversation, as applicable.
14. The circumstances of the consent process minimize the possibility of coercion or undue influence.

13 FDA-Regulated Research

FDA regulations apply to research that involves a FDA-regulated *test article* in a *clinical investigation* involving *human subjects* as defined by the FDA regulations. For FDA-regulated research, the IRB must apply the FDA regulations at 21 CFR 50 and 21 CFR 56. If required by organizational policy or a FWA, 45 CFR 46 must also be applied.

Clinical trials with investigational drugs must be conducted according to FDA's IND regulations, 21 CFR Part 312, and other applicable FDA regulations. Use of an investigational device in a clinical trial to obtain safety and effectiveness data must be conducted according to FDA's IDE regulations, 21 CFR Part 812, and other applicable FDA regulations. If the research is conducted or supported by a Common Rule agency or department, or if compliance with the Common Rule is required by state law or the terms of an award or contract, then the Common Rule must also be applied.

The following procedures describe the review of FDA-regulated research conducted under the auspices of HMH.

13.1 Definitions

Biologic. Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other technologies. In general, the term "drugs" includes therapeutic biological products.

Dietary Supplement. A dietary supplement is a product taken by mouth that is intended to supplement the diet and that contains a dietary ingredient. The dietary ingredients in these products can include vitamins, minerals, herbs and other botanicals, amino acids, other dietary substances intended to supplement the diet, and concentrates, metabolites, constituents, extracts, or combinations of the preceding types of ingredients. See section 201(ff) of the FD&C Act [21 U.S.C. 321(ff)].

Investigational Drug. Investigational *or* experimental drugs are new drugs that have not yet been approved by the FDA or approved drugs that are being studied in a clinical investigation.

Investigational Device. Investigational device means a device (including a transitional device) that is the object of an investigation. Investigation, as it pertains to devices, means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.

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

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

In Vitro Diagnostic Product (IVD). In vitro diagnostic products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. [21 CFR 809.3(a)]

Emergency Use. Emergency use is defined as the use of an investigational 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. [21CFR 56.102(d)]

Significant Risk (SR) Device. 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) Device. A non-significant risk device is an investigational device that does not meet the definition of a significant risk device.

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

13.2 FDA Exemptions

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

1. Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review. [21 CFR §56.104(c)]
2. Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the FDA 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)]

13.3 Procedures

A. At initial submission, the investigator must indicate whether the research involves a test article and is a clinical investigation involving human subjects on the application form. The investigator may use the Research Determination Checklist to assist in making this determination.

B. During the pre-review process, the RIO Manager will confirm whether FDA regulations are applicable using the Research Determination Worksheet If FDA regulations apply and the research is not exempt, the RIO Manager will indicate on the agenda that the study is FDA-regulated.

C. If the study involves investigational drugs and is industry sponsored and required by the sponsor, the investigator will indicate on the application form that ICH-GCP E6 compliance is required and provide an affirmation of compliance. HMH follows ICH-GCP E6 to the extent it is consistent with FDA regulations. If the study involves investigational drugs and is industry sponsored and the PI has not indicated ICH-GCP E6 compliance, the RIO Manager will review the study to determine if ICH-GCP E6 applies and obtain investigator affirmation of compliance, if needed.

13.4 Investigator Responsibilities

The investigator holds additional responsibilities when conducting a clinical trial evaluating FDA-regulated drugs, devices, and other articles. These responsibilities include, but are not limited to, the following:

1. The investigator is responsible for ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs (including biological products) or agreement for clinical investigations of medical devices, the investigational plan and other applicable regulations, and any requirements imposed by the IRB or FDA.
2. The investigator is responsible for personally conducting or supervising the investigation. When certain study-related tasks are delegated by an investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.
3. The investigator must maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated. This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks (e.g., it can refer to an individual's CV on file and/or training conducted by the investigator/sponsor), and identify the dates of involvement in the study. An investigator should maintain separate lists for each study conducted by the investigator.
4. The investigator is responsible for protecting the rights, safety, and welfare of subjects under their care during a clinical trial. This responsibility includes:

- Informing subjects that the test articles is being used for investigational purposes and ensuring that the requirements relating to obtaining informed consent are met
- Providing reasonable medical care for study subjects for medical problems arising during participation in the trial that are, or could be, related to the study intervention
- Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual (e.g., when the investigator is unavailable, or when specialized care is needed)
- Adhering to the protocol/research plan so that study subjects are not exposed to unreasonable risks
- As appropriate, informing the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and the subject agrees to the primary physician being informed

5. The investigator is responsible for reading and understanding the information in the investigator brochure or device risk information, including the potential risks and side effects of the drug or device.
6. The investigator is responsible for maintaining adequate and accurate records in accordance with FDA regulations and to making those records available for inspection by the FDA. These records include: correspondence with other investigators, the IRB, the sponsor, monitors, or the FDA; drug and device accountability records; case histories; consent forms; and documentation that consent was obtained prior to any participation in the study. Records must be obtained for a minimum of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such. Other regulations, such as HIPAA, organizational policies, or contractual agreements with sponsors may necessitate retention for a longer period of time. Prior to destroying records, PI's should contact the Research Integrity Office for further guidance.
7. The investigator is responsible for controlling drugs, biological products, and devices according to FDA regulations and the Controlled Substances Act, if applicable.
8. The investigator proposing the clinical investigation will be required to provide a plan – to be evaluated by the IRB - that includes storage, security, and dispensing of the test article.
    a. The investigator is responsible for investigational drug accountability that includes storage, security, dispensing, administration, return, disposition, and records of accountability. Such details will be provided in the IRB submission and reviewed by the IRB and the Pharmacy Service for acceptability.
    b. The investigator may delegate in writing, as part of the IRB submission, the responsibility detailed in 'a' above to the Pharmacy Service.

c. All devices received for a study must be stored in a locked environment under secure control with limited access. Proper instructions on the use of the device must be provided to the subjects. A log must be kept regarding the receipt, use, and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation.

9. The investigator shall furnish all reports required by the sponsor of the research including adverse events, progress reports, safety reports, final reports, and financial disclosure reports.
10. The investigator will permit inspection of research records by the sponsor, sponsor representatives, HRPP and IRB representatives, the FDA, accrediting bodies, and any other agencies or individuals entitled to inspect such records under regulation, organizational policy, or contractual agreement.

13.5 Dietary Supplements

Research involving dietary supplements may or may not fall under FDA regulations. Under the Dietary Supplement Health and Education Act (DSHEA) of 1994, a dietary supplement is not considered a drug and is not subject to the premarket approval requirements for drugs if the intended use for which it is marketed is only to affect the structure or any function of the body (i.e., not intended to be used for a therapeutic purpose). Whether a study falls under FDA oversight is determined by the intent of the clinical investigation. If the clinical investigation is intended only to evaluate the dietary supplement's effect on the structure or function of the body, FDA research regulations do not apply. However, if the study is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, then FDA regulations do apply. Studies involving the ingestion of dietary supplements that are not subject to FDA oversight are still research, and therefore must be reviewed by the IRB.

Similarly, whether an IND is needed for a study evaluating a dietary supplement is determined by the intent of the study. If the study is intended only to evaluate the dietary supplement's effect on the structure or function of the body, an IND is not required. However, if the study is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required under part 312.

As with any research involving a test article, the investigator must supply the IRB with sufficient information to determine that the criteria for approval are satisfied and to determine or verify whether or not the research requires an IND. Applications should provide detail consistent with that expected on a drug protocol/research plan and consistent with the level of risk associated or anticipated with the research. At a minimum, the research plan should provide the following information regarding the supplement: Name, Manufacturer, Formulation, Dosage, Method/Route of Administration, Mechanism of Action, Known Drug Interactions, Risk Profile, IND number (or justification for why an IND is unnecessary), documentation of approval for use in humans, documentation or certification of Quality or Purity. As with drugs and devices there should be an accountability plan for the product describing where the product will be stored

and how it will be dispensed, usage tracked, and disposal or return. If the study entails greater than minimal risk, a plan for Data and Safety Monitoring must be included.

13.6 Clinical Investigations of Drugs and Devices

13.6.1 IND/IDE Requirements

For studies evaluating the safety or effectiveness of medical devices or experiments using drugs, biologics, dietary supplements, and other compounds that may be considered a drug under FDA regulations, the investigator must indicate on the IRB application whether or not an IDE or IND is in place, and, if not, the basis for why an IDE or IND is not needed. Documentation must be provided by the sponsor or the sponsor-investigator. Documentation of the IND/IDE could be a:

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

For investigational devices, the study may be exempt from IDE requirements or, in the case of Non-significant Risk (NSR) device studies, follow abbreviated IDE requirements which do not require formal approval by the FDA. If a sponsor has identified a device study as exempt or NSR, then the investigator should include documentation with the submission providing the basis for exempt or NSR categorization. If the FDA has determined that the study is exempt or NSR, documentation of that determination must be provided.

The IRB will review the application and, based upon the documentation provided, determine: (1) that there is an approved IND/IDE in place, (2) that the FDA has determined that an IND is not required or that a device study is exempt or NSR, or, (3) if neither of the above, whether or not an IND is necessary, or that a device study is exempt or NSR, using the criteria below. The IRB cannot grant approval to the research until the IND/IDE status is determined, and, if necessary, an approved IND or IDE is in place. Please Note: An IND goes into effect 30 days after the FDA receives the IND, unless the sponsor receives earlier notice from the FDA.

13.6.1.1 IND Exemptions

For drugs, an IND is not necessary if the research falls in one of the following seven (7) categories:

1. The drug being used in the research is lawfully marketed in the United States and all of the following requirements are met:
    a. The research is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug

   b. In the case of a prescription drug, the research is not intended to support a significant change in the advertising for the product;
   c. The research does not involve a route of administration, dose, 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;
   d. The research is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
   e. The research is conducted in compliance with the requirements of 21 CFR 312.7 (i.e., the research is not intended to promote or commercialize the drug product); and
   f. The research does not intend to invoke FDA regulations for planned emergency research [21 CFR 50.24].
2. The research only involves one or more of the following: (a) Blood grouping serum, (b) Reagent red blood cells or (c) Anti-human globulin;
3. For clinical investigations involving an in vitro diagnostic biological product, an IND is not necessary if a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and b) it is shipped in compliance with 312.160
4. A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.
5. Bioavailability or Bioequivalence (BA/BE) studies if all of the following conditions are met:
   a. The drug product does not contain a new chemical entity [21 CFR 314.108], is not radioactively labeled, and is not cytotoxic;
   b. The dose (single dose or total daily dose) does not exceed the dose specified in the labeling of the approved version of the drug product;
   c. The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively]; and
   d. The sponsor meets the requirements for retention of test article samples [21 CFR 320.31(d)(1)] and safety reporting [21 CFR 320.31(d)(3)].
6. Research using a radioactive drug or biological product if all of the following conditions are met:
   a. It involves basic research not intended for immediate therapeutic, diagnostic, or similar purposes, or otherwise to determine the safety and efficacy of the product;
   b. The use in humans is approved by a Radioactive Drug Research Committee (RDRC) that is composed and approved by FDA;
   c. The dose to be administered is known not to cause any clinically detectable pharmacological effect in humans, and
   d. The total amount of radiation to be administered as part of the study is the smallest radiation dose practical to perform the study without jeopardizing the benefits of the study and is within specified limits.
7. FDA practices enforcement discretion for research using cold isotopes of unapproved drugs if all of the following conditions are met:

a. The research is intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a drug labeled with a cold isotope or regarding human physiology, pathophysiology, or biochemistry;
b. The research is not intended for immediate therapeutic, diagnostic, or preventive benefit to the study subject;
c. The dose to be administered is known not to cause any clinically detectable pharmacologic effect in humans based on clinical data from published literature or other valid human studies;
d. The quality of the cold isotope meets relevant quality standards; and
e. The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively].

13.6.1.2 IDE Exemptions

For clinical investigations of devices, an IDE is not 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 (a “501k” device);
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.

13.6.1.3 Significant and Non-Significant Risk Device Studies

A device study is a Non-Significant Risk (NSR) Device study if it is not IDE exempt and does not meet the definition of a Significant Risk (SR) Device study.

Under 21 CFR 812.3(m), an SR device means an investigational device that:

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

If the FDA has already determined a study to be SR or NSR, documentation evidencing such should be provided to the IRB as described in Section 13.6.1. The FDA's determination is final and the IRB does not have to make the device risk determination.

Unless the FDA has already made a device risk determination for the study, the IRB will review studies that the sponsor or investigator have put forth as NSR at a convened meeting to determine if the device represents SR or NSR.

The sponsor or sponsor-investigator is responsible for providing the IRB with an explanation describing the basis for their initial determination of NSR and any other information that may help the IRB in evaluating the risk of the study (e.g., reports of prior investigations of the device).

The IRB will review the information provided by the sponsor and investigator including, but not limited to: the sponsor or investigator's NSR assessment, the description of the device, reports of prior investigations of the device (if applicable), the proposed investigational plan, and subject selection criteria.

The NSR/SR determination made by the IRB will be based on the proposed use of the device in the investigation, not on the device alone. The IRB will consider the nature of any harms that may result from use of the device, including potential harms from additional procedures subjects would need to undergo as part of the investigation (e.g., procedures for inserting, implanting, or deploying the device). The IRB may consult with the FDA or require the sponsor or investigator to obtain a determination from the FDA. The IRB will document the SR or NSR determination and the basis for it in the meeting minutes and provide the investigator, and sponsor when applicable, with the determination in writing.

Non-significant risk device studies do not require submission of an IDE application to the FDA but must be conducted in accordance with the abbreviated requirements of IDE regulations (21 CFR 812.2(b)). Under the abbreviated requirements, the following categories of investigations

are considered to have approved applications for IDE's, unless FDA has notified a sponsor under 812.20(a) that approval of an application is required:

> (1) An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor (or sponsor-investigator):
>
> > (i) Labels the device in accordance with 812.5;
> >
> > (ii) Obtains IRB approval of the investigation after presenting the reviewing IRB with an explanation of why the device is not a significant risk device, and maintains such approval;
> >
> > (iii) Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under 56.109(c).
> >
> > (iv) Complies with the requirements of 812.46 with respect to monitoring investigations;
> >
> > (v) Maintains the records required under 812.140(b) (4) and (5) and makes the reports required under 812.150(b) (1) through (3) and (5) through (10);
> >
> > (vi) Ensures that participating investigators maintain the records required by 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7); and
> >
> > (vii) Complies with the prohibitions in 812.7 against promotion and other practices.

When the FDA or IRB determines that a study is SR, the IRB may approve the study, but the study cannot begin until an IDE is obtained.

13.7 Humanitarian Use Devices

A Humanitarian Use Device (HUD) is an approved (marketed) medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 8,000 individuals in the United States per year [21 CFR 814.3(n)]. Federal law requires that IRBs approve the use of an HUD at a facility. Once approved, the clinical use of the HUD may be considered as any other approved device, with the caution that effectiveness has not been shown in clinical trials.

13.7.1 Definitions

Humanitarian Device Exemption. A Humanitarian Device Exemption (HDE) is a "premarket approval application" submitted to FDA pursuant to Subpart A, 21 CFR Part 814 "seeking a humanitarian device exemption from the effectiveness requirements of sections 514 and 515 of the [FD&C Act] as authorized by section 520(m)(2) of the [FD&C Act]." HDE approval is based upon, among other criteria, a determination by FDA that the HUD will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from use

of the device outweighs the risk of injury or illness from its use while taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

HDE Holder. An HDE Holder is a person who or entity that obtains to approval of an HDE from the FDA.

13.7.2 IRB Review Requirements

A Humanitarian Use Device (HUD) may only be used in a facility after an IRB has approved its use, except in certain emergencies. The HDE holder is responsible for ensuring that a HUD is provided only to facilities having an IRB constituted and acting in accordance with the FDA's regulations governing IRBs (21 CFR Part 56), including continuing review of use of the device.

When a HUD is used in a clinical investigation (i.e., research involving one or more subjects to determine the safety or effectiveness of the HUD), the full requirements for IRB review and informed consent apply (21 CFR 50 and 56) as well as other applicable regulations. It is essential to differentiate whether the HUD is being studied for the indication(s) in its approved labeling or for different indication(s). When the HUD is being studied for the indication(s) in its approved labeling, the IDE regulations at 21 CFR 812 do not apply. However, when the HUD is being studied for a different indication(s), 21 CFR 812 does apply, including the requirement for a FDA-approved IDE before starting the clinical investigation of a Significant Risk device.

13.7.3 Procedures

The relevant requirements and procedures for investigators and for IRB review described elsewhere in this manual apply to clinical investigations of HUDs. The material within this section applies to diagnostic or treatment uses of HUDs.

The health care provider seeking approval for diagnostic or treatment use of a HUD at HMH is responsible for obtaining IRB approval prior to use of the HUD at the facility and for complying with the applicable regulations, including those for medical device reporting, institutional policies, and the requirements of the IRB.

Health care providers seeking initial IRB approval for diagnostic or treatment use of a HUD for the indication(s) in the HUDs approved labeling should submit the following materials to the IRB:

1. Application Form – Humanitarian Use Devices (non-research uses)
2. A copy of the HDE approval letter from the FDA
3. A description of the device, such as a device brochure
4. The patient information packet for the HUD
5. The proposed clinical consent process
6. Other relevant materials (e.g., training certificates) as identified in the Application Form

The IRB will review the initial proposal at a convened meeting ensuring that appropriate expertise is available either within the membership in attendance or via the use of consultants.

The IRB will review the risks to patients that are described in the product labeling and other materials, the proposed procedures to ensure that risks are minimized, and will evaluate whether the risks are reasonable in relation to the potential benefits to patients at the facility. The IRB will evaluate the patient information packet and proposed consent process and will determine if the materials are adequate and appropriate for the patient population.

The IRB may specify limitations on the use of the device, require additional screening and follow up procedures, require interim reports to the IRB, require continuing review more often than annually, or set other conditions or requirements as appropriate to minimize risks to patients and ensure the safe use of the device in the facility.

Once use of the HUD is approved, the health care provider is responsible for submitting any proposed changes to the IRB-approved plan or patient materials and obtaining approval for those changes prior to implementation, unless the change is necessary to avoid or mediate an apparent immediate risk to a patient. The IRB may review these changes using expedited review procedures or refer the changes for review by the convened IRB.

The health care provider is responsible for submitting reports to the FDA, the IRB, and the manufacturer/HDE Holder whenever a HUD may have caused or contributed to a death, and must submit reports to the manufacturer (or to FDA and the IRB if the manufacturer is unknown) whenever a HUD may have caused or contributed to a serious injury (21 CFR 803.30 and 814.126(a)). Serious injury means an injury or illness that (1) is life-threatening, (2) results in permanent impairment of a bodily function or permanent damage to a body structure, or (3) necessitates medical or surgical intervention to preclude permanent impairment of a bodily function or permanent damage to a body structure (21 CFR 803.3). The specific requirements for this reporting are in the Medical Device Reporting (MDR) Regulation, at 21 CFR Part 803. The IRB will review these reports via either expedited or convened review, as appropriate, and will consider whether any changes are needed to the IRB-approved plan or patient materials.

The health care provider is responsible for submitting continuing review materials to the IRB sufficiently in advance of the expiration date to ensure IRB review and re-approval prior to expiration. Materials to be submitted include:

1. The Continuing Review Report – Humanitarian Use Devices (non-research uses)
2. Any safety reports or summaries provided by the HDE holder that had not previously been submitted
3. The current patient information packet, if applicable
4. The current consent, if applicable
5. Other materials as identified on the Continuing Review Report
6. Any other new relevant information or materials

The IRB may conduct continuing review using expedited review procedures because the HDE-approved HUD is a legally marketed device and no safety and effectiveness information is being systematically collected or review by the convened IRB.

13.7.4 Emergency Uses of HUDs

If an appropriately trained and licensed health care provider in an emergency situation determines that IRB approval for the use of the HUD at the facility cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be used without prior IRB approval. The health care provider must, within 5 days after the emergency use of the device, provide written notification of the use to the IRB including the identification of the patient involved, the date of the use, and the reason for the use.

If a HUD is approved for use in a facility, but an appropriately trained and licensed health care provider wants to use the HUD outside its approved indication(s) in an emergency or determines that there is no alternative device for a patient's condition, the physician should consult with the HDE holder and IRB in advance if possible, obtain informed consent if possible, and ensure that reasonable measures are taken to protect the well-being of the patient such as a schedule and plan for follow up examinations and procedures to monitor the patient, taking into consideration the patient's specific needs and what is known about the risks and benefits of the device. The provider should submit a follow up report to the HDE holder and the IRB and must comply with medical device reporting requirements.

The IRB may require additional reports, patient protection measures, or other requirement, as appropriate given the specifics of the situation.

13.8 Expanded Access to Investigational Drugs, Biologics, and Devices

Expanded access pathways, also referred to as "compassionate use", are designed to make investigational medical products available as early in the drug and device evaluation process as possible to patients without therapeutic options, because they have exhausted or are not a good candidate for approved therapies and cannot enter a clinical trial. Expanded access refers to access to investigational medical products outside of a clinical trial, where the intent is treatment, rather than research. Because the investigational products have not yet been approved by FDA as safe and effective, it is important to remember that the product may not be effective and there may be unexpected serious adverse effects and to take appropriate measures to ensure that this is understood by the patient or their representative and to monitor for safety.

13.8.1 Expanded Access to Investigational Drugs and Biologics

The FDA's expanded access rule for investigational drugs, including biologics classified as drugs, is intended to improve access to investigational drugs, and approved drugs with limited availability under a risk evaluation and mitigation strategy (REMS), for patients with serious or immediately life-threatening diseases or conditions who lack other therapeutic options and may benefit from the investigational diagnostic or therapy.

Under the FDA's expanded access rule, access to investigational drugs for treatment purposes will be available to:

- Individual patients, including in emergencies [21 CFR 312.310]

- Intermediate-size patient populations [21 CFR 312.315]
- Larger populations under a treatment protocol or treatment IND [21 CFR 312.320]

Expanded access submissions are categorized by FDA as either "Access Protocols", which involve a protocol amendment to an existing IND, or "Access INDs", which are managed separately from any existing INDs.

The FDA has also established a rule, "Charging for Investigational Drugs Under an Investigational New Drug Application", to:

- Provide general criteria for authorizing charging for an investigational drug [21 CFR 312.8(a)]
- Provide criteria for charging for an investigational drug in a clinical trial [21 CFR 312.8(b)]
- Set forth criteria for charging for an investigational drug under the expanded access for treatment use
- Clarify what costs can be recovered

Investigators, when seeking access to drugs under the expanded access provisions, should work closely with the sponsor or manufacturer, the FDA, and the HMH HRPP, to determine the appropriate access mechanism and ensure that proper regulatory procedures are followed.

Unless the conditions that permit an emergency use exemption (see Section 13.9) are satisfied, prospective IRB review and approval is required for all expanded access uses, including clinical patient use. This requires, among other things, that the IRB review the expanded access use through the expedited review procedures.

13.8.2 Expanded Access to Investigational and Unapproved Medical Devices

As with investigational drugs, unapproved medical devices may normally only be used in humans in an approved clinical trial under the supervision of a participating clinical investigator. However, there may be circumstances under which a health care provider may wish to use an unapproved device when a patient is facing life-threatening circumstances or suffering from a serious disease or condition for which no other alternative therapy or diagnostic exists or is a satisfactory option for the patient.

FDA has made the following mechanisms available for these circumstances:

- Emergency Use
- Planned Emergency Research (See Section 11.11.1)
- Compassionate Use (or Single Patient/Small Group Access)
- Treatment Use
- Continued Access

Investigators, when seeking access to investigational or unapproved devices under one of the above provisions, should work closely with the sponsor or manufacturer, the FDA, and the HMH Manager, Research Integrity Office to ensure that proper regulatory procedures are followed.

Unless the conditions that permit an emergency use exemption are satisfied (see Section 13.9), prospective IRB review and approval is required. This requires, among other things, that the IRB review the proposed use through the expedited review procedures.

13.9 Emergency Use

If an appropriately trained and licensed health care provider in an emergency situation determines that IRB approval for the use of an investigational drug/device at the facility cannot be obtained in time to prevent serious harm or death to a patient, the drug or device may be used without prior IRB approval. The health care provider must, within 5 days after the emergency use of the drug or device, provide written notification of the use to the IRB including the identification of the patient involved, the date of the use, and the reason for the use.

Note: DHHS regulations do not permit 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 Part 46. However, nothing in the DHHS regulations at 45 CFR Part 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.

13.9.1 Emergency Exemption from Prospective IRB Approval

Under FDA regulations [21 CFR 56.104(c)], FDA exempts the emergency use of a test article from the requirement for prospective IRB approval, provided that such emergency use is reported to the IRB within 5 working days. The emergency use of a test article, other than a medical device, is a clinical investigation, the patient is a participant, and the FDA may require data from an emergency use to be reported in a marketing application. Any subsequent use of the test article in the facility requires IRB review. However, FDA acknowledges that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

FDA defines emergency use as the use of a test article 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 [21 CFR 56.102(d)]. If all conditions described in 21 CFR 56.102(d) exist then the emergency exemption from prospective IRB approval found at 21 CFR 56.104(c) may be used.

Life-threatening, for the purposes of 21 CFR 56.102(d), includes both life-threatening and severely debilitating.

Unless the provisions for an emergency exception from the informed consent requirement are satisfied (see Section 13.9.2), informed consent must be obtained in accordance with 21 CFR 50 and documented in writing in accordance with 21 CFR 50.27.

The IRB must be notified within 5 working days when an emergency exemption is used. The designated IRB personnel will review the report to verify that circumstances of the emergency use conformed to FDA regulations. This must not be construed as an approval for the emergency use by the IRB, as an exemption from the requirement for prospective IRB approval has been invoked. When appropriate, in the event a manufacturer requires documentation from the IRB, the IRB will provide a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). *Optional:* Reports of emergency uses will be brought to the convened IRB for their information.

Investigators are reminded that they must comply with all other organizational policies and requirements applicable to the use of the investigational or unapproved article.

13.9.2 Emergency Exception from the Informed Consent Requirement

An exception under FDA regulations at 21 CFR 50.23(a-c) permits the emergency use of an investigational or unapproved test article without informed consent where the investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing all four of the following specific conditions:

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

If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent physician determination in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

The IRB must be notified within 5 working days when an emergency exception is used. The designated IRB member will review the report to verify that circumstances of the emergency exception conformed to FDA regulations.

13.9.3 Waiver of Informed Consent for Planned Emergency Research

HMH IRB follows FDA regulations, 21 CFR 50.24, and any applicable state requirements which permit waiver of informed consent requirements for emergency research when human subjects in need of emergency medical intervention cannot provide legally effective informed consent and their legally authorized representatives (LARs) are also unable or unavailable to give informed consent on their behalf.

See Section 11.11.1 for additional detail on Planned Emergency Research.

14 Reportable Events

Regulations require an organization to have written procedures for ensuring prompt reporting of changes in research activity; unanticipated problems involving risk to subjects or others (UPIRTSOs); and any instances of serious or continuing non-compliance to the IRB, organizational officials, and applicable federal agencies. The various types of reportable events should be reported on the appropriate form within the electronic submission system (Unanticipated Problem/SAE, Protocol deviations/violations/non-compliance). In order to comply with this requirement, HMH has procedures to review issues that arise during the conduct of research.

Section 14.2 addresses procedures for evaluating and reporting external safety reports for Sponsors.

The following section provides definitions and procedures regarding issues that arise during the conduct of research that must be reported to the IRB.

14.1 Definitions

Unanticipated problems involving risk to participants or others. Unanticipated problems involving risks to subjects or others (UPs/UAPs/UPIRTSOs) refer to any incident, experience, outcome, or new information that:

1. Is unexpected; **and**
2. Is related or possibly related to participation in the research; **and**
3. Indicates that subjects or others are at a greater risk of harm (including physical, psychological, economic, legal or social harm) than was previously known or recognized.

Unexpected. The incident, experience or outcome is not expected (in terms of nature, severity, or frequency) given the research procedures that are described in the study-related documents, such as the IRB-approved research protocol/research plan and informed consent documents; and the characteristics of the subject population being studied.

Related. There is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research.

Adverse Event. For the purposes of these policies and procedures, an adverse event (AE) is any untoward or unfavorable 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. Adverse events encompass both physical and psychological harms. They occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research.

Unanticipated Adverse Device Effect. An Unanticipated Adverse Device Effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in

nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety, or welfare of subjects [21 CFR 812.3(s)].

Protocol/Research Plan Deviations. A protocol/research plan deviation is defined as a variation from the IRB approved research plan that happens without prior review and approval of the IRB (e.g., study visit outside protocol/research plan window, blood work drawn outside protocol/research plan window, etc.). Depending on the details, protocol/research plan deviations may be determined to be non-compliance (serious, continuing, or otherwise).

Protocol/Research Plan Exceptions. Protocol/research plan exceptions are planned deviations from the protocol/research plan. Exceptions are anticipated and must occur with prior agreement from the sponsor, if applicable, and approval by the IRB. If an exception is implemented without IRB approval, it is a deviation, even when the sponsor has approved.

Protocol Non-Compliance. Non-compliance is defined as failure to adhere to federal, state, or local regulations governing human subject research, organizational policies related to human subject research, or the requirements or determinations of the IRB. Non-compliance may be minor or sporadic or it may be serious or continuing.

14.2 Procedures for Reporting Unanticipated Problems/Adverse Events

14.2.1 When the HMH IRB is NOT the IRB of Record (Use of an external IRB)

For events occurring in subjects enrolled in a multicenter studies (i.e. MedWatch, CIOMs, SUSARs, other expedited reports) that are distributed routinely to investigators or IRBs at all institutions conducting research, Hackensack Meridian Health will **not** review or retain these types of reports. This includes accessing sponsor web portals. Should the sponsor, or HMH Sponsor–Investigator (if applicable) ascertain through their assessments of these reports that an unanticipated problem involving risk to subjects or others exists and that there are implications for the protocol, the report(s) and the related protocol, consent, investigational brochure, changes will be submitted to the IRB of record. The events must meet the criteria as established in section 14.1.

Any event occurring uniquely at Hackensack Meridian Health **must be reported** to the HMH IRB in addition to the external IRB of Record, as indicated in Section 9.1.3. Such events occurring uniquely at HMH meeting criteria in Section 9.1.3, must immediately be provided to the Institutional Official, Chief Compliance Officer, the PI's Department Chair, and the Vice-President of Research upon receipt of information from the reviewing IRB or the study team. HMH will work collaboratively with the external IRB, following applicable responsibilities of an authorization agreement/arrangement, and take any necessary action in addressing the reportable event on a site-specific level.

The Sponsor's or HMH Sponsor–Investigator's report will include a clear explanation of why the adverse event or series of adverse events have been determined to be an unanticipated

problem; and (2) the implications for the conduct of the trial (i.e. requiring a significant and usually related safety related change in the protocol and/or the consent).

14.2.2 When the HMH IRB is the IRB of Record

Unless specifically required by the HMH IRB (e.g. first in human clinical trials), the HMH IRB does not accept reports of adverse events and IND Safety Reports that do not meet the criteria of an unanticipated problem involving risks to subjects or others (See Section 14.1). However, adverse events in clinical trials conducted at HMH or by a HMH investigator must be reported to the sponsor in compliance with FDA regulations and sponsor requirements, regardless of whether it is reported to the HMH IRB.

Deaths of HMH patients that meet the criteria in 14.1 require immediate (within 24 hours) reporting. Other deaths may be reported in aggregate at the time of continuing review.

If investigators are uncertain but believe that the event might qualify as an unanticipated problem, a report should be submitted.

The HMH IRB must also be informed of the following events or issues as soon as possible, but in no instance, later than 10 working days after the investigator first learns of the event.

1. A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).
2. A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy.)
3. Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment group's reveals higher rate in the drug treatment arm versus a control). A summary and analyses supporting the determination should accompany the report.
4. An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to human subjects. A discussion of the divergence from the expected specificity or severity should accompany the report.

5. A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison). A discussion of the divergence from the expected rate should accompany the report.
6. Changes made to the research without prior IRB approval to eliminate apparent immediate hazards to the subject(s).
7. Adverse events involving direct harm to subjects enrolled by the investigator either local or external), which in the opinion of the investigator or sponsor, may represent an unanticipated problem involving risk to subjects or others.
8. An unanticipated event related to the research that exposes subjects to potential risk but that does not involve direct harm to subjects (e.g. lost laptop).
9. An unanticipated event related to the research that results in actual harm or exposes individuals other than the research participants (e.g., investigators, research assistants, students, the public, etc.) to potential risk.
10. IND Safety Reports from sponsors that meet the criteria for an unanticipated problem involving risk to subjects.
11. Data and Safety Monitoring Reports that indicate that risks are greater than previously known or that indicate that the study requires modification or should be suspended or terminated.
12. New information that indicates an increase to the risks or decrease to potential benefits of the research. Examples include:
    - 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
    - a paper is published from another study that shows that the risks or potential benefits of the research may be different than initially presented to the IRB.
13. New information that may impact the willingness of participants to continue in the research.
14. A breach of confidentiality.
15. Incarceration of a participant in a study not approved to enroll prisoners.
16. Complaint of a subject when the complaint involves the health, safety, or rights of the subject or indicates unexpected risks, possible non-compliance, or cannot be resolved by the research team.
17. Protocol/research plan deviations.
18. Changes made to the research without prior IRB approval in order to eliminate apparent immediate harm.

19. Sponsor or lead investigator/coordinating center imposed suspension or termination of some or all research activities.
20. Unanticipated adverse device effects (UADEs). (Note: Regulations require that UADEs be reported to the sponsor and IRB as soon as possible but in no event later than 10 working days after the investigator first learn of the event [21 CFR 812.150(a)(1)]).
21. Any other adverse event or safety finding (e.g. based on animal or epidemiologic data) that indicates subjects or others might be at risk of serious, unanticipated harms that are reasonably related to the research. These would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects. An explanation of the conclusion should accompany the report.

14.2.3 Unanticipated problems/adverse events that do not meet reporting criteria

For unanticipated problems/adverse events associated with clinical trials that do not meet the criteria in Section 14.1, the investigator or study team member should describe the events at the time of continuing review.

14.2.4 Protocol Deviations

Protocol deviations should be reported to the HMH, using the reportable event form in the electronic research submission system, only when the deviation placed subjects or others at a greater risk of harm (including physical, psychological, economic, legal or social harm) than was previously known or recognized.

14.2.5 Protocol Non-Compliance

Non-Compliance. Non-compliance, as defined in Section 14.1, must be reported to the HMH IRB as soon as the principal investigator or research staff become aware of the event(s).

15 Unanticipated Problems Involving Risks to Subjects or Others

HMH complies with DHHS and FDA regulations which require organizations to have written policies on reporting unanticipated problems involving risks to subjects or others (UP/UAP/UPRIRTSO) to the IRB, organizational officials and relevant federal agencies and departments.

The following procedures describe how UAPs are handled in research under the auspices of HMH. Unless specifically required by the IRB, the HMH IRB does not accept reports of adverse events that do not meet the definition of an UAP.

15.1 IRB Review

Upon receipt of the Reportable Event Form from an investigator, the IRB staff checks the form for completeness. If any applicable sections of the form are incomplete or have been answered unsatisfactorily, the IRB staff will return the form to the investigator or the designated contact person to make revisions or provide additional information.

If the IRB Office staff believes that immediate intervention may be required to protect participants or others from serious harm, reports will be forwarded to the RIO Manager or designee.

Upon receipt of a report or complaint of from someone other than the investigator or study staff on behalf of the investigator, the RIO Manager will notify the investigator when appropriate.

The IRB Chair or an experienced member(s) designated by the IRB Chair receives and reviews the report. The IRB Chair (or designee) will make the initial determination as to whether the event is to be regarded as an unanticipated problem and/or non-compliance (See Section 16 for non-compliance review procedures).

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 and must follow notification procedures for IRB suspensions. At the time of suspension, available information about the situation should be provided to the Institutional Official, Vice-President of Research, the PI's Department Chair, and the Chief Compliance Officer. The report should be updated after the IRB meeting following reporting procedures in Section 18 of these SOPs.

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

If the IRB Chair or designee determines that the problem does not possibly meet the definition of an unanticipated problem or serious or continuing non-compliance, the reviewer will consider whether any corrective or preventative actions are sufficient and whether modifications to the research plan, consent, or corrective action plan may be necessary, and refer the matter to the convened IRB for review if appropriate. The results of the review will be recorded in the study record and communicated to the investigator.

If the reviewer determines that the event represents an unanticipated problem involving risk to subjects or others (UAP), the report will be placed on the agenda for the next convened IRB meeting.

The IRB will be given access to the study file, the currently approved consent document, previous reports of UAPs, the investigator's brochure (if one exists), the event report, and recommendations from the IRB Chair or designee, when appropriate.

After review of the study and event report, the full IRB will make findings and recommendations based on the following considerations:

- Whether the reported event is a UAP according to the definition in this policy.
- What action in response to the report is appropriate.
- Whether suspension or termination of approval is warranted.

1. If the IRB finds that the event is not a UAP, according to the definition in the policy, the IRB may recommend any of the following actions:
    a. No action
    b. Requiring modifications to the protocol/research plan
    c. Revising the continuing review timetable
    d. Modifying the consent process
    e. Modifying the consent document
    f. Providing additional information to current participants (e.g., whenever the information may relate to the subject's willingness to continue participation)
    g. Providing additional information to past subjects
    h. Requiring additional training of the investigator and/or study staff
    i. Other actions as appropriate given the specific circumstances
2. If the IRB finds that the event is a UAP, according to the definition in the policy, the IRB may recommend any of the following actions:
    a. Requiring modifications to the protocol/research plan
    b. Revising the continuing review timetable
    c. Modifying the consent process
    d. Modifying the consent document
    e. Providing additional information to current participants (e.g., whenever the information may relate to the subject's willingness to continue participation)
    f. Providing additional information to past participants
    g. Requiring additional training of the investigator and/or study staff
    h. Reconsidering approval
    i. Requiring that current subjects re-consent to participation
    j. Monitoring the research

k. Monitoring consent

l. Referral to other organizational entities (e.g., legal counsel, risk management, Institutional Official)

m. Suspending the research approval

n. Terminating the research approval

o. Other actions as appropriate given the specific circumstances

3. If a report suggests that participant safety is at risk, the IRB may immediately suspend or terminate the research. Any suspension or termination of research by the IRB must be promptly reported to the Institutional Official, Chief Compliance Officer, the PI's Department Chair, and Vice-President of Research, as well as relevant federal regulatory agencies through the IO. This should be done in writing.
4. If, after reviewing a report, the IRB finds that the event is a UAP or that suspension or termination of approval is warranted, the IRB will:
    a. Notify the investigator in writing of its findings, with copies to the Chair of the investigator's department and/or research unit, other affected units and the investigator's supervisor, and
    b. Report its findings and recommendations to the Vice President for Research for further reporting to the appropriate federal officials (see Section 18).

16 Non-compliance

As part of its commitment to protecting the rights and welfare of human subjects in research, HMH reviews all reports and allegations of non-compliance and takes any necessary action to ensure the ethical conduct of research.

All Investigators and other study personnel involved in human subject research are required to comply with all laws and regulations governing their research activities, as well as with requirements and determinations of the IRB.

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

16.1 Definitions

Non-compliance. Non-compliance is defined as failure to adhere to federal, state, or local regulations governing human subject research, organizational policies related to human subject research, or the requirements or 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 non-compliance that, in the judgment of the convened IRB, creates an increase in risks to subjects, adversely affects the rights, welfare or safety of subjects, or adversely affects the scientific integrity of the study. Willful violation of regulations and/or policies may also constitute serious non-compliance.

Continuing non-compliance. Continuing non-compliance is defined as a pattern of non-compliance that, in the judgment of the convened IRB, suggests a likelihood that instances of non-compliance will continue unless the IRB or organization intervenes.

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/research plan 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.) Once a finding of non-compliance is proven, it must be categorized as minor non-compliance, serious, sporadic or continuing.

16.2 Reporting

Investigators and their study staff are required to report instances of possible non-compliance. The investigator is responsible for reporting any possible non-compliance by study personnel to the IRB. However, any individual or employee may report observed or apparent instances of non-compliance to the HMH IRB. In such cases, the reporting party is responsible for making these reports in good faith, maintaining confidentiality and cooperating with any IRB and/or organizational review of these reports.

If an individual, whether investigator, study staff or other, is uncertain whether there is cause to report non-compliance, he or she may contact the RIO Manager or Chair directly to discuss the situation informally.

Reports of non-compliance must be submitted to the IRB Office within 10 working days of discovery of this non-compliance. The report must include a complete description of the non-compliance including any personnel involved.

Complainants may choose to remain anonymous.

16.3 Review of Allegations of Non-compliance

All allegations of non-compliance will be reviewed by the IRB Chair or designee, who will review the report or allegation and may request additional information or an audit of the research in question.

When the Chair or designee determines that non-compliance did not occur because the incident was within the limits of an approved protocol/research plan for the research involved, the determination is reported in writing to the investigator and, if applicable, the reporting

party. The determination letter will be copied to the Institutional Official in cases where the Institutional Official and any other parties had been notified of the allegation at the outset.

If in the judgment of the IRB Chair or designee, the report or allegation does represent non-compliance, the non-compliance will be processed according to Section 16.4 (Review of Findings of Non-compliance).

If in the judgment of the IRB Chair or designee, 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 as described in Section 8 with subsequent review by the IRB.

The Chair or designee may determine that additional expertise or assistance is required to make these determinations and may request assistance from HRPP or IRB personnel or form an *ad hoc* committee to assist with the review and fact gathering process. When an *ad hoc* committee assists in the review process, the Chair or designee is responsible for assuring that minutes of the meeting are generated and kept to help support any determinations or findings made by the *ad hoc* committee.

16.4 Review of Findings of Non-compliance

16.4.1 Non-compliance that is not serious or continuing:

When the Chair or designee determines that the non-compliance occurred, but the non-compliance does not meet definition of serious or continuing non-compliance, the determination is reported in writing to the investigator and, if applicable, the reporting party. The Chair will review any corrective and preventative actions taken or proposed by the investigator and determine if the actions are sufficient or if additional actions may be necessary. In the event that additional actions may be warranted, the matter will be referred to the convened IRB for review.

16.4.2 Serious or Continuing Non-compliance

When the Chair or designee determines that non-compliance has occurred and that the non-compliance may meet the definition of serious or continuing non-compliance, the report of non-compliance is referred for review by the IRB at the next available convened meeting. However, the Chair or designee may use discretion and call an emergency IRB meeting should the circumstances warrant an urgent meeting.

All initial findings of potential serious or continuing non-compliance referred to the IRB will be reviewed at a convened meeting.

At this stage, the IRB may:

1. Find that there is no issue of non-compliance
2. Find that there is non-compliance that is neither serious nor continuing and that an adequate corrective and/or preventive action plan is in place

3. Find that there is serious or continuing non-compliance and modify or require a corrective and/or preventive action plan
4. Find that additional information is required to make a final determination. In this instance, the committee will request additional information, and indicate whether such information will be reviewed by the full committee or a subcommittee thereof; if the latter, a report will be written by the subcommittee for review by the full committee for final determination.

16.4.3 **Final Review**

The IRB will make a final determination as to whether the non-compliance is serious or continuing. Upon a finding of serious or continuing non-compliance, the IRB's possible actions could include, but are not limited to:

1. Request a corrective and/or preventive action plan from the investigator
2. Verification that subject selection is appropriate
3. Observation of informed consent
4. Require an increase in data and safety monitoring of the research activity
5. Request a directed audit of areas of concern
6. Request a status report after each participant receives intervention
7. Modify the continuing review cycle
8. Require additional investigator and staff education
9. Notify current subjects (e.g., if the information about the non-compliance might affect their willingness to continue participation)
10. Require modification of the protocol/research plan.
11. Require modification of the information disclosed during the consent process.
12. Require current subjects to re-consent to participation.
13. Suspend the study (See below); or
14. Terminate the study (See below)

In cases where the IRB determines that the event of non-compliance also meets the definition of unanticipated problem involving risks to subjects or others, it will be handled according to Section 15.

The investigator is informed of the IRB determination and the basis for the determination in writing. 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 18.

17 Complaints

The HRPP Director or designee will promptly handle, and, if necessary, investigate all complaints, concerns, and appeals received by the Research Integrity Office. This includes complaints, concerns, and appeals from investigators, research participants and others.

All complaints, written or oral (including telephone complaints), and regardless of point of origin, are recorded in writing and forwarded to the Chief Compliance Officer.

Upon receipt of the complaint, the RIO Manager and the Director of the Human Research Protection Program, in consultation with the IRB 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 8 will be followed.

If the complaint may meet the definition of non-compliance, it will be considered an allegation of non-compliance according to Section 16.

If the complaint may meet the definition of an unanticipated problem involving risk to subjects or others, it will be handled according to Section 15.

If the complaint is actually a query from a subject regarding study procedures, payments not received, etc., it will be forwarded to the investigator/study team for handling. The investigator/study team will be required to inform the IRB when the matter is closed (and the subject is satisfied with the answer).

Within 3 business days of receipt of the complaint, the RIO Manager or the Director of the Human Research Protection Program will generate a letter to acknowledge that the complaint has been received and is being investigated, if the person making the complaint provided contact information. The Corporate Compliance office, the Institutional Official, the PI's Department Chair, and the Vice-President of Research will be notified of any complaints that meet the definition of non-compliance.

18 Reporting to Regulatory Agencies and Organizational Officials

Federal regulations require prompt reporting to appropriate organizational officials and, as applicable, the federal department or agency head or the FDA, of (i) any unanticipated problems involving risks to subjects or others; (ii) any serious or continuing non-compliance with this policy or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval. HMH IRB complies with this requirement as follows.

18.1 Procedures

1) IRB staff will initiate these procedures as soon as the IRB takes any of the following actions:

a. Determines that an event may be considered an unanticipated problem involving risks to participants or others

b. Determines that non-compliance was serious or continuing

c. Suspends or terminates approval of research

2) The Director of the Human Research Protection Program 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 IRB 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 investigator on the project

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/research plan, 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 the earlier of

1. A specific date

2. When an investigation has been completed or a corrective action plan has been implemented

3) The IRB Chair and the IO review the letter and recommend modifications as needed.

4) The Institutional Official is the signatory for all correspondence from the facility.

5) The RIO Manager sends a copy of the report to:

a. The IRB by including the letter in the next agenda packet as an information item

b. The Institutional Official

c. The following federal agencies:

- OHRP, if the study is subject to DHHS regulations or subject to a DHHS FWA.
- FDA, if the study is subject to FDA regulations.
- If the study is conducted or funded by any Federal Agency other than DHHS that is subject to "The Common Rule", the report is sent to OHRP or the head of the federal agency as required by the agency.

- Reporting to a regulatory agency is not required if the event occurred at a site that was not subject to the direct oversight of the organization, and the agency has been notified of the event by the investigator, sponsor, another organization, or other mechanisms.

d. Investigator

e. Sponsor, if the study is sponsored

f. Chairman or supervisor of the investigator

g. The Privacy Officer of a covered entity, if the event involved unauthorized use, loss, or disclosure of individually-identifiable patient information from a covered entity

h. The Chief Information Security Officer of an organization, if the event involved violations of information security requirements of that organization

i. Office of Risk Management, if appropriate

j. Others as deemed appropriate by the Institutional Official

The RIO Manager ensures that all steps of this policy are completed within 30 working days of the determination. For more serious actions, the RIO Manager will expedite reporting.

19 Investigator Responsibilities

Investigators are ultimately responsible for the conduct of research. Investigators may delegate tasks to appropriately trained and qualified members of their research team. However, investigators must maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibilities.

19.1 Investigators

The research team is made up of 'investigators', differentiated as follows, along with their responsibilities in the conduct of research involving human participants.

Principal Investigators (PI)

At HMH individuals with admitting privileges or who are employed at HMH may serve as the PI or as the faculty sponsor on a research project involving human subjects.

Adjunct faculty of the Organization and any investigator whose status is considered to be "in training" (e.g., students and medical residents and fellows) may not serve as a PI but may serve as a Sub-investigator. PIs will ensure that research designed and conducted by trainees has sound research design and is appropriately supervised.

The IRB recognizes one PI for each study. The PI has ultimate responsibility for the research activities.

Studies that require expertise or skills beyond those held by the PI must either be modified or have expertise and skills supplemented by the inclusion of one or more additional qualified sub-investigators.

Sub-Investigators

A sub-investigator is any individual other than the PI who is involved in the conduct of a research study. Such involvement could include:

- Obtaining information about living individuals by intervening or interacting with them for research purposes;
- Obtaining identifiable private information about living individuals for research purposes;
- Obtaining the voluntary informed consent of individuals to be subjects in research; and
- Studying, interpreting, or analyzing identifiable private information or data for research purposes.

19.2 Responsibilities

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;
2. Develop a research plan that is scientifically sound and minimizes risk to the subjects;
3. Incorporate into the research plan a plan to ensure the just, fair, and equitable recruitment and selection of subjects;
4. When some or all of the subjects are likely to be vulnerable to coercion or undue influence(e.g., children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons), include additional safeguards in the study to protect the rights and welfare of these subjects;
5. Ensure that the research plan includes adequate provisions for the monitoring of subjects and data to ensure the safety of subjects;
6. Ensure that there are adequate provisions to protect the privacy interests of subjects;
7. Ensure that there are adequate provisions to protect data confidentiality and interests of subjects, including an information security plan that considers the collection, storage, maintenance, analysis, and transmission of data and other identifiable information;
8. Have sufficient resources necessary to protect human subjects, including:
    a. Access to a population that would allow recruitment of the required number of subjects.
    b. Sufficient time to conduct and complete the research.

c. Adequate numbers of qualified staff.

d. Adequate facilities.

e. Necessary equipment.

f. A plan to ensure proper supervision of the research including a plan for periods of absence or decreased availability.

g. Availability of medical, psychological, or other support that subjects might require during or as a consequence of their participation in the research.

9. 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 New Jersey and the policies of HMH;

10. Assure that all study personnel are educated in the regulatory requirements regarding the conduct of research and the ethical principles upon which they are based;

11. Assure that all persons assisting with the research are adequately trained and informed about the protocol/research plan and their specific duties and functions.

12. Promptly report any changes in, addition to, or departure of investigators or research staff to the IRB for evaluation and approval (note that investigators and staff may not begin work on the research until IRB-approved);

13. Protect the rights, safety, and welfare of participants;

14. Ensure that when private health information is used, legally effective HIPAA authorization is obtained for each subject unless the Privacy Board or IRB has approved a waiver of the requirement;

15. Ensure that the language in the consent form is consistent with that in the protocol/research plan and, when applicable, in the HIPAA authorization;

16. Obtain and document informed consent and ensure that no human subject is involved in the research prior to obtaining consent or consent/permission from their legally authorized representative, unless a waiver of the requirement has been approved by the IRB;

17. Have a procedure to receive questions, complaints, or requests for additional information from subjects and respond appropriately;

18. Ensure that all information provided to the IRB is accurate and complete so that the IRB may fulfill its responsibilities to review the research and make the required determinations;

19. Ensure that all research involving human subjects receives IRB review and approval in writing or a determination of exemption before research begins;

20. Ensure that all research involving human subjects is reviewed by other experts and organizational components and committees as applicable to the research;

21. Comply with all IRB decisions, conditions, and requirements;

22. Ensure that studies receive timely continuing IRB review and approval;
23. Report unanticipated problems, deviations, complaints, non-compliance, suspensions, terminations, and any other reportable events to the IRB;
24. Notify the IRB if information becomes available that suggests a change to the potential risks or benefits of the research
25. Obtain IRB review and approval before changes are made to the research unless a change is necessary eliminate apparent immediate hazards to the subject(s);
26. Seek HRPP or IRB assistance when in doubt about whether proposed research requires IRB review;
27. Retain records for the time period and in the manner required by applicable regulations, contractual agreements, and organizational policies.

Additional investigator responsibilities, including specific responsibilities for investigators engaged in FDA-regulated research are described elsewhere in this document.

19.3 Investigator Records

Under these policies investigators must maintain, at a minimum but not limited to, the following research records under these policies. In addition, investigators must also comply with all record-keeping sponsor requirements.

19.3.1 Study Records

- Individual subject records
- Recruitment materials
- Documentation of consent process (who, what, when and how)
- Signed consent forms
- Unanticipated Problem & Reportable Event Reports
- Subject complaint reports
- Results of all procedures conducted on the subject, including final visit (if no final visit, reason why: e.g., removal from study, withdrawal from study, death)

19.3.2 Regulatory Records

- Most recent IRB-approved protocol/research plan
- Previous versions of protocol/research plan
- All correspondence (i.e., approvals, reporting forms and responses, etc.) to and from the IRB
- All correspondence with the sponsor and others regarding the study

- Continuing review progress reports
- Modification Requests
- Investigational product accountability records, when applicable

19.3.3 **Record Retention**

Investigator records must be retained in accordance with regulatory, organizational and sponsor or grantor requirements:

Type of Record	Minimum Retention Period
IRB Records	3 years after study completion
Federal Grants	3 years after expiration of grant period
HIPAA Authorization	6 years after completion of study
HIPAA Waiver	6 years after completion of study
FDA	2 years after last marketing approval

All records must be maintained securely with limited access. Disposal of investigator records must be done in such a manner that no identifying information can be linked to research data.

19.4 Investigator Concerns

Investigators who have concerns or suggestions regarding HMH's HRPP or IRB(s) should convey them to the Institutional Official, Chief Compliance Officer, or via the Compliance Hotline or other responsible parties (e.g., supervisor, departmental Chair), when appropriate. The Institutional Official will consider the issue, and when deemed necessary, seek additional information and convene the parties involved to form a response for the investigator or make necessary procedural or policy modifications, as warranted. In addition, the Chair of the IRB or the RIO Manager will be available to address investigators' questions, concerns and suggestions.

In addition to these SOPs, which are made available on the HMH website for investigators, investigators are also made aware of the process for expressing their concerns via statement on approval letters, link on the HMH website for concerns or complaints.

20 Sponsored Research

It is HMH policy that any sponsored research conducted under the auspices of the Organization 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.

20.1 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 (public, industry, or private) through a grant or contract that involves a specified statement of work (e.g., the research proposal), including clinical trials involving investigational drugs, devices or biologics.

20.2 Responsibility

Sponsor grants, contracts, and other written agreements will be reviewed for the following by the Research Contracts Office within the Office of Research Administration, with consultation with the IRB, as necessary:

1. All sponsor contracts have a written agreement with the Sponsor that addresses medical care for research participants with a research-related injury, when appropriate.
2. In studies where Sponsors conduct research site monitoring visits or conduct monitoring activities remotely, the sponsor contracts have a written agreement with the Sponsor that the Sponsor promptly reports (no longer than within 30 days) to the HMH findings that could affect the safety of participants or influence the conduct of the study.
3. When the Sponsor has the responsibility to conduct data and safety monitoring, the sponsor contracts have a written agreement with the Sponsor that addresses provisions for monitoring the data to ensure the safety of participants and for providing data and safety monitoring reports to the HMH.
4. Sponsor contracts have a written agreement with the Sponsor about plans for disseminating findings from the research and the roles that investigators and Sponsors will play in the publication or disclosure of results.
5. When participant safety could be directly affected by study results after the study has ended, the sponsor contracts have a written agreement with the Sponsor that the investigator or HMH will be notified of the results in order to consider informing participants. The Sponsor's reporting obligation shall continue for two years following completion of the study conducted under the contract.
6. Payment in exchange for referrals of prospective participants from investigators (physicians) ("finder's fees") is not permitted. Similarly payments designed to accelerate recruitment that are tied to the rate or timing of enrollment ("bonus payments") are also not permitted.

21 Conflict of Interest in Research

It is HMH policy to preserve public trust in the integrity and quality of research by reducing actual or perceived conflict of interest in the conduct of research.

Conflicts of interest ('COI') in research can be broadly described as any interest that competes with an organization's or individual's obligation to protect the rights and welfare of research subjects, the integrity of a research study, or the credibility of the research program. Conflicts of interest can be financial or non-financial.

In the environment of research, openness and honesty are indicators of integrity and responsibility, characteristics that promote quality research and strengthen the research process. Therefore, conflicts of interest should be eliminated when possible and effectively managed and disclosed when they cannot be eliminated.

21.1 Researcher Conflicts of Interest

Pursuant to the Conflict of Interest policy *"Research COI Policy*, HMH maintains a Conflict of Interest Committee ("COI Committee"). The HMH RIO collaborates with the COI Committee to ensure that COI of researchers and research staff ('researchers') are identified and managed before the IRB completes its review of any research application.

21.1.1 Procedures

21.1.1.1 Disclosure of Researcher COI

For IRB purposes, researcher conflict review occurs at the time of new study submission, continuing review, with the addition of a new researcher, and whenever a researcher updates their HMH COI disclosure indicating a new or changed interest. The COI Coordinator reviews the researchers' disclosures and either notifies the IRB staff that no researcher COI was identified or that one or more researchers has an interest that requires evaluation by the COI Committee. In the event a conflict that requires disclosure or management is identified, the COI Coordinator will provide to the IRB in writing with a summary of conflict and the conflict management plan ('CMP') approved by the COI Committee. If the COI Committee has not completed its review, the IRB will defer the research study review or prohibit participation by the researcher with a potential COI until the COI Committee review process is completed and the results are made available to the IRB.

Conflict of interest or conflict of commitment-who is looking at it and making determinations?

21.1.1.2 Evaluation of COI

The IRB will review COI and CMP to determine:

- Whether the COI affects the rights or welfare of research subjects,
- Whether the COI might adversely affect the integrity or credibility of the research or the research program, and
- Whether the CMP effectively protects research subjects and the integrity and credibility of the research and the research program

The IRB will consider:

- How the research is supported or financed,
- The nature and extent of the conflict,
- The role and responsibilities of the conflicted individual in the design, conduct, and reporting of the research, and
- The ability of the conflicted individual to influence the outcome of the research

21.1.1.3 Management of COI

The IRB has final authority to determine whether the research, the COI, and the CMP, if any, allow the research to be approved. With regard to the CMP issued by the COI Committee, the IRB shall either affirm or request changes to strengthen it. The IRB can require additional measures to manage a COI so that the research may be approved. However, the IRB cannot weaken a CMP approved by the COI Committee.

For example, in addition to the CMP, the IRB may require:

1. Disclosure of the COI to subjects through the consent process
2. Modification of the research plan or safety monitoring plan
3. Monitoring of research by a third party
4. Disqualification of the conflicted party from participation in all or a portion of the research
5. Appointment of a non-conflicted PI
6. Divestiture of significant financial interests
7. Severance of relationships that create actual or potential conflicts.

In the event the conflict cannot be effectively managed, the IRB may disapprove the research.

21.1.2 IRB Member Conflict of Interest

No IRB member or alternate may participate in the review of any research project in which the member has a conflict of interest (COI), except to provide information as requested. It is the responsibility of each IRB member to disclose any COI related to a study submitted for review and recuse him/herself from the deliberations and vote by leaving the room.

For example, all members and alternate members of the IRB complete a "yearly disclosure" along with a yearly recusal agreement when first appointed and annually thereafter or sooner when their circumstances change. These forms are submitted to Research Integrity Office, who determines if a COI exists. To protect the privacy of members, the specific details of the conflict will not be given to staff or other members; however, the type of research where a COI exists will be provided (e.g., all studies from X sponsor; studies using X device/drug; studies involving X investigator). The IRB staff, in turn, ensures that IRB members and alternates are not assigned to conduct reviews of studies for which the member has a conflict and to ensure appropriate

recusal during convened meetings. IRB staff may consult with Corporate Compliance to clarify whether a specific study involves a member COI.

IRB members, alternates, or consultants may be considered to have a conflicting interest requiring recusal when they, or an immediate member of their family, have any of the following:

1. Involvement in the design, conduct, and reporting of the research,
2. Significant financial interests (See *Research COI Policy]* for a definition of significant financial interests) related to the research being reviewed,
3. Any other situation where an IRB member believes that another interest conflicts with his or her ability to deliberate objectively on a study.

The IRB Chair will ask IRB members at the beginning of each convened meeting if any members have a COI regarding any of the items to be reviewed and reminds members that they must recuse themselves by leaving the room during the discussion and vote of the specific research study. If a conflicted member is participating by conference call, videoconference or web meeting, the member's participation (connection) is terminated for discussion and voting.

IRB members with a conflicting interest are excluded from being counted towards quorum. Recusals of members with COIs are recorded in the minutes.

21.2 Institutional Conflict of Interest

An institutional conflict of interest in research ("Institutional COI") describes a situation in which the financial interests of an institution or an institutional official, acting within his or her authority on behalf of the institution, may unduly affect or appear to affect the conduct of research or other related activities of the institution. Institutional COI's are of concern when institutional financial interests create the potential for inappropriate influence over the institution's activities. HMH outlines the mechanism to deal with organizational conflict in the Institutional Conflict of Interest Policy. This policy is intended to protect against risks to research integrity, research participants and the mission that may result from Institutional COI's in research. The purpose of this policy is to promote the highest ethical standards in the conduct of research in situations where institutional conflicts of interest may occur, and to determine those instances when an Institutional COI's are unacceptable.

21.3 Recruitment Incentives

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

22 Participant Outreach

HMH 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 HMH and provide them the opportunity to provide input and express concerns.

The following procedures describe how HMH fulfils that responsibility.

22.1 Responsibility

It is the responsibility of the RIO Manager to implement the procedures outlined below.

22.2 Outreach Resources and Educational Materials

1. The Office of Research Administration dedicates a section of the website to research participants. This website includes resources, such as Frequently Asked Questions (FAQs), HMH designed brochures (such as Volunteering in Research), and a listing of relevant research-related links.
2. The participant web page includes information regarding how to contact HMH with any questions or concerns about specific research projects or research in general.
3. The participant web page includes a "Contact Us" link that allows members of the community to ask questions, express concerns, or provide feedback. Provision of contact information by the person is optional.
4. HMH periodically provides presentations related to research to community organizations.

22.3 Evaluation

On an annual basis, HMH evaluates its outreach activities and makes changes when appropriate. In order to formally evaluate its outreach activities, the RIO Manager and Education Coordinator will review:

1. The specific community outreach activities being used
2. Whether or not these community outreach activities have an evaluative component (e.g., evaluation instrument distributed to participants), and if so whether the feedback was positive, negative, or neutral and if any suggestions were made that could be used to enhance future activities.
3. The number of times the participant web page is visited
4. Feedback provided via the "Contact Us" mechanism on the participant web page.
5. Feedback provided from other sources (unaffiliated IRB members, investigators, research staff, students, etc.)

The results of the review 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.

23 Health Insurance Portability and Accountability Act (HIPAA)

The *Health Insurance Portability and Accountability Act of 1996* (HIPAA) required the creation of a Privacy Rule for identifiable health information. While the primary impact of the Privacy Rule is on the routine provision of and billing for health care, the Rule also affects the conduct and oversight of research.

The Privacy Rule defines individually identifiable health information transmitted or maintained by a covered entity in any form (electronic, written or oral) as "protected health information" (PHI) and establishes the conditions under which investigators may access and use this information in the conduct of research.

Except as otherwise permitted, the Privacy Rule requires that a research subject "authorize" the use or disclosure of his/her PHI to be used in research. This authorization is distinct from the subject's consent to participate in research, which is required under the Common Rule and FDA regulations.

Under the Privacy Rule, a HIPAA Authorization may be combined with the consent document for research. When the consent document is combined with an Authorization as it is at HMH, 45 CFR part 46 and 21 CFR part 56 require IRB review of the combined document.

At HMH, for exempt projects and other categories of research not subject to IRB or Privacy Board oversight, the HRPP Office is designated to act upon requests for waivers and alterations of the Authorization requirement for research purposes.

23.1 Definitions (per HIPAA Privacy Booklet for Research)

Access. Access is the mechanism of obtaining or using information electronically, on paper, or other medium for the purpose of performing an official function.

Accounting of Disclosures. Information that describes a covered entity's disclosures of PHI other than for treatment, payment, and health care operations; disclosures made with Authorization; and certain other limited disclosures. For those categories of disclosures that need to be in the accounting, the accounting must include disclosures that have occurred during the 6 years (or a shorter time period at the request of the individual) prior to the date of the request for an accounting. However, PHI disclosures made before the compliance date for a covered entity are not part of the accounting requirement.

Authorization. An individual's written permission to allow a covered entity to use or disclose specified PHI for a particular purpose. Except as otherwise permitted by the Privacy Rule, a covered entity may not use or disclose PHI for research purposes without a valid Authorization.

Covered entity. A health plan, a health care clearinghouse, or a health care provider who transmits health information in electronic form in connection with a transaction for which DHHS has adopted a standard.

Data Use Agreement. An agreement into which the covered entity enters with the intended recipient of a limited data set that establishes the ways in which the information in the limited data set may be used and how it will be protected.

Designated Record Set. A group of records maintained by or for a covered entity that includes (1) medical and billing records about individuals maintained by or for a covered health care provider; (2) enrollment, payment, claims adjudication, and case or medical management record systems maintained by or for a health plan; or (3) used, in whole or in part, by or for the covered entity to make decisions about individuals. A record is any item, collection, or grouping of information that includes PHI and is maintained, collected, used, or disseminated by or for a covered entity.

Disclosure. The release, transfer, access to, or divulging of information in any other manner outside the entity holding the information.

Health Information. Health Information means any information, whether oral or recorded in any form or medium, that (1) is created or received by a health care provider, health plan, public health authority, employer, life insurer, school or university, or health care clearinghouse; and (2) 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 the past, present, or future payment for the provision of health care to an individual.

Individually Identifiable Health Information. Information that is a subset of health information, including demographic information collected from an individual, and (1) is created or received by a health care provider, health plan, employer, or health care clearinghouse; and (2) relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; and (a) that identifies the individual; or (b) with respect to which there is a reasonable basis to believe the information can be used to identify the individual.

Limited Data Set. Refers to PHI that excludes 16 categories of direct identifiers and may be used or disclosed, for purposes of research, public health, or health care operations, without obtaining either an individual's Authorization or a waiver or an alteration of Authorization for its use and disclosure, with a data use agreement.

Minimum Necessary. The standard that uses the least information reasonably necessary to accomplish the intended purpose of the use, disclosure, or request. Unless an exception applies, this standard applies to a covered entity when using or disclosing PHI or when requesting PHI from another covered entity. A covered entity that is using or disclosing PHI for research without Authorization must make reasonable efforts to limit PHI to the minimum necessary. A covered entity may rely, if reasonable under the circumstances, on documentation of IRB or Privacy Board approval or other appropriate representations and documentation under section 164.512(i) as establishing that the request for protected health information for the research meets the minimum necessary requirements.

Privacy Board. A board that is established to review and approve requests for waivers or alterations of Authorization in connection with a use or disclosure of PHI as an alternative to obtaining such waivers or alterations from an IRB. A Privacy Board consists of members with varying backgrounds and appropriate professional competencies as necessary to review the effect of the research plan on an individual's privacy rights and related interests. The board must include at least one member who is not affiliated with the covered entity, is not affiliated with any entity conducting or sponsoring the research, and is not related to any person who is affiliated with any such entities. A Privacy Board cannot have any member participating in a review of any project in which the member has a conflict of interest.

Protected Health Information. PHI is individually identifiable health information transmitted by electronic media, maintained in electronic media, or transmitted or maintained in any other form or medium. PHI excludes individually identifiable health information in education records covered by the Family Educational Rights and Privacy Act, as amended, 20 U.S.C. 1232g, records described at 20 U.S.C. 1232g(a)(4)(B)(iv), and employment records held by a covered entity in its role as employer.

Research. A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. This includes the development of research repositories and databases for research.

Use. With respect to individually identifiable health information, the sharing, employment, application, utilization, examination, or analysis of such information within the entity or health care component (for hybrid entities) that maintains such information.

Waiver or Alteration of Authorization. The documentation that the covered entity obtains from an investigator or an IRB or a Privacy Board that states that the IRB or Privacy Board has waived or altered the Privacy Rule's requirement that an individual must authorize a covered entity to use or disclose the individual's PHI for research purposes.

Workforce. Employees, volunteers, trainees, and other persons whose conduct, in the performance of work for a covered entity, is under the direct control of the covered entity, whether or not they are paid by the covered entity.

23.2 The IRB's Role under the Privacy Rule

Under the Privacy Rule, IRBs gained authority to consider, and act upon, requests for a partial or complete waiver or alteration of the Privacy Rule's Authorization requirement for uses and disclosures of PHI for research. Although DHHS and FDA Protection of Human Subjects Regulations include protections to help ensure the privacy of subjects and the confidentiality of information, the Privacy Rule supplements these protections by requiring covered entities to implement specific measures to safeguard the privacy of PHI. If certain conditions are met, an IRB may grant a waiver or an alteration of the Authorization requirement for research uses or disclosures of PHI.

HMH has designated the HMH IRB to fulfill the functions of a Privacy Board for human subject research.

The Privacy Rule does not change the composition of an IRB. The Privacy Rule permits a covered entity to accept documentation of waiver or alteration approval from any qualified IRB or Privacy Board -- not only the IRB overseeing the organization's research.

When acting upon a request to waive or alter the Authorization requirement, an IRB must follow the procedural requirements of the DHHS Protection of Human Subjects regulations and, if applicable, FDA regulations, including using either the normal review procedures (review by the convened IRB) or the expedited review procedures.

When a request for a waiver or an alteration of the Authorization requirement is considered by the convened IRB, a majority of the IRB members must be present at the meeting, including at least one member whose primary concerns are in nonscientific areas. In order for an approval of a waiver or an alteration of the Privacy Rule's Authorization requirement to be effective, it must be approved by a majority of the IRB members present at the convened meeting. If a member of the IRB has a conflicting interest with respect to the PHI use and disclosure for which a waiver or an alteration approval is being sought, that member may not participate in the review. Expedited review of a request for a waiver or an alteration of the Authorization requirement is permitted where the research activity qualifies for expedited review under Common Rule requirements. In addition, 45 CFR 46.110 and 21 CFR 56.110 permit an IRB to use an expedited review procedure to review minor changes in previously approved research. A modification to a previously approved research plan, which only involves the addition of an Authorization for the use or disclosure of PHI to the IRB-approved informed consent, may be reviewed by the IRB through an expedited review procedure, because this type of modification may be considered to be no more than a minor change to research. If expedited review procedures are appropriate for acting on the request, the review may be carried out by the IRB Chair or by one or more experienced reviewers designated by the Chair from among the IRB members. A member with a conflicting interest may not participate in an expedited review. If an IRB uses expedited review procedures, it must adopt methods for keeping all its members advised of requests for waivers or alterations of the Authorization requirement as well as those requests that have been granted under an expedited review procedure. IRB documentation of approval of a waiver or alteration of the authorization requirement includes:

- The identity of the approving IRB
- The date on which the waiver or alteration was approved
- A statement that the IRB has determined that all the specified criteria for a waiver or an alteration were met
- A brief description of the PHI for which use or access has been determined by the IRB to be necessary in connection with the specific research activity
- A statement that the waiver or alteration was reviewed and approved under either normal or expedited review procedures
- The required signature of the IRB Chair or the Chair's designee.

HMH will not release PHI to investigators without individual authorization or proper documentation of an IRB or Privacy Board approval of a waiver or alteration of the requirement. In order to ensure that appropriate approvals are in place and that uses of patient information for research are in accordance with HMH standards, HMH does not accept waivers or alterations approved by a non-HMH Privacy Board or IRB without review and approval of the requested disclosure by the HMH HRPP.

23.3 Authorization

Except as otherwise permitted, the Privacy Rule requires that a research subject "authorize" the use or disclosure of his/her PHI to be used in research. This authorization is distinct from the subject's consent to participate in research, which is required under the Common Rule and FDA regulations. Just as a valid consent under Common Rule and FDA regulations must meet certain requirements, a valid authorization must contain certain statements and core elements [45 CFR 164.508(c)]. At HMH authorization language is to be incorporated into the consent document. Template consent documents, which include HIPAA authorization language, are available from the HRPP.

Once executed, a signed copy must be provided to the individual providing authorization. Signed authorizations must be retained by the covered entity for 6 years from the date of creation or the date it was last in effect, whichever is later.

A research subject has the right to revoke their authorization at any time. Investigators are not required to retrieve information that was disclosed under the authorization before learning of the revocation. Additionally, investigators may continue to use and disclosure PHI already obtained for the research under an authorization to the extent necessary to protect the integrity of the research.

When an authorization is obtained for research purposes, the Privacy Rule requires that it pertain only to a specific research study, not to nonspecific research or to future, unspecified projects. The Privacy Rule considers the creation and maintenance of a research repository or database as one specific research activity, the subsequent use or disclosure by a covered entity of information from the database for a specific research study requires separate authorization unless a waiver of the requirement is granted.

When an Authorization permits disclosure of PHI to a person or organization that is not a covered entity (such as a sponsor or funding source), the Privacy Rule does not continue to protect the PHI disclosed to such entity. However, other federal and state laws and agreements between the covered entity and recipient such as a Business Associate Agreement (BAA) or Confidentiality Agreement may establish continuing protections for the disclosed information. Under the DHHS Protection of Human Subjects regulations or the FDA Protection of Human Subjects regulations, an IRB may impose further restrictions on the use or disclosure of research information to protect subjects.

Authorization Core Elements:

1. A description of the PHI to be used or disclosed, identifying the information in a specific and meaningful manner.
2. The names or other specific identification of the person or persons (or class of persons) authorized to make the requested use or disclosure.
3. The names or other specific identification of the person or persons (or class of persons) 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 expiration event that relates to the individual or to the purpose of the use or disclosure ("end of the research study" or "none" are permissible for research, including for the creation and maintenance of a research database or repository).
6. Signature of the individual and date. If the individual's legally authorized representative signs the Authorization, a description of the representative's authority to act for the individual must also be provided.

Authorization Required Statements:

1. A statement of the individual's right to revoke his/her Authorization and how to do so, and, if applicable, the exceptions to the right to revoke his/her Authorization or reference to the corresponding section of the covered entity's notice of privacy practices.
2. Whether treatment, payment, enrollment, or eligibility of benefits can be conditioned on Authorization, including research-related treatment and consequences of refusing to sign the Authorization, if applicable.
3. A statement of the potential risk that PHI will be re-disclosed by the recipient. This may be a general statement that the Privacy Rule may no longer protect health information disclosed to the recipient.

23.4 Waiver or Alteration of the Authorization Requirement

Obtaining signed authorization to access and use of PHI for research is not always feasible. The Privacy Rule contains criteria for waiver or alterations of authorization. If a covered entity has used or disclosed PHI for research pursuant to a waiver or alteration of authorization, documentation of the approval of the waiver or authorization must be retained for 6 years from the date of its creation or the date it was last in effect, whichever is later.

For research uses and disclosures of PHI, an IRB or Privacy Board may approve a waiver or an alteration of the authorization requirement in whole or in part. A complete waiver occurs when the IRB or Privacy Board determines that no authorization will be required for a covered entity to use and disclose PHI for a particular research project. A partial waiver of authorization occurs when the IRB or Privacy Board determines that a covered entity does not need authorization for all PHI uses and disclosures for research purposes, such as accessing PHI for research

recruitment purposes. An IRB or Privacy Board may also approve a request that removes some PHI, but not all, or alters the requirements for an authorization (an alteration).

In order for an IRB or Privacy Board to waive or alter authorization, the Privacy Rule (45 CFR 164.512(i)(2)(ii)) requires the IRB or Privacy Board to determine the following:

1. The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
    a. An adequate plan to protect health information identifiers from improper use and disclosure.
    b. An adequate plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a healthcare or research justification for retaining them or a legal requirement to do so).
    c. Adequate written assurances that the PHI will not be reused or disclosed to (shared with) 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 Privacy Rule.
2. The research could not practicably be conducted without the waiver or alteration.
3. The research could not practicably be conducted without access to and use of the PHI.

The Privacy Rule allows institutions to rely on a waiver or an alteration of Authorization obtained from a single Privacy Board to be used to obtain or release PHI in connection with a multi-site project. However, DHHS also recognizes that "covered entities may elect to require duplicate Privacy Board reviews before disclosing [PHI] to requesting researchers" (67 *Federal Register* 53232, August 14, 2002). At HMH, PHI may not be disclosed for the purposes of research pursuant to a waiver provided by a non-HMH Privacy Board without the approval of the HRPP or IRB.

23.5 Activities Preparatory to Research

Under the preparatory to research provision of the Privacy Rule, a covered entity may permit an investigator who works for that covered entity to use PHI for purposes preparatory to research such as assessing the feasibility of conducting a research project, developing a grant application, or identifying potential subjects. A covered entity may also permit, as a disclosure of PHI, a researcher who is not a workforce member of that covered entity to review PHI (within that covered entity) for purposes preparatory to research.

The covered entity must obtain from an investigator representations that (1) the use or disclosure is requested solely to review PHI as necessary to prepare a research plan or for

similar purposes preparatory to research, (2) the PHI will not be removed from the covered entity in the course of review, and (3) the PHI for which use or access is requested is necessary for the research.

At HMH, this is accomplished by the investigator submitting either a Preparatory to Research form (for projects in development) or a request for waiver of consent and authorization for screening purposes to the HRPP Office.

23.6 Research Using Decedent's Information

The HRPP Office obtains from the investigator:

(A) Representation that the use or disclosure sought is solely for research on the protected health information of decedents; (B) Documentation, at the request of the covered entity, of the death of such individuals; and (C) Representation that the protected health information for which use or disclosure is sought is necessary for the research purposes.

23.7 Future Uses: Databases and Repositories

The Privacy Rule recognizes the creation of a research database or a specimen repository to be a research activity if the data/specimens to be stored contain PHI. There are two separate activities that the covered entity must consider: (1) the use or disclosure of PHI for creating a research database or repository and (2) the subsequent use or disclosure of PHI in the database for a particular research plan.

Individual authorization for the storage of PHI for future research must be sought unless the IRB has determined that the criteria for a waiver of the authorization requirement are satisfied. See Section 23.4 of this policy manual for a discussion of waivers of authorization.

At HMH, consent for research and authorization for use and/or disclosure of PHI are combined in one document. As with any research activity, the combined consent/authorization for future research must describe the future research uses in sufficient detail to allow the potential subject to make an informed decision. The investigator and IRB should be cognizant of uses of information/specimens that the target community may consider particularly sensitive, such as genetics, mental health, studies of origin, and use of tissues that may have cultural significance.

The consent/authorization for future research can be a stand-alone document or may be incorporated into another consent/authorization if the information/specimens will originate from another research activity, such as a clinical trial, unless the research involves the use or disclosure of psychotherapy notes. Authorizations for the use or disclosure of psychotherapy notes can only be combined with another authorization for a use or disclosure of psychotherapy notes.

If the consent/authorization for future research is combined with another research consent/authorization, the consent/authorization must clearly differentiate between the research activities and allow the individual to opt-in to the future research. Opt-outs for future

research are not permitted under the Privacy Rule because an opt-out process does not provide individuals with a clear ability to authorize the use of their information/specimens for future research, and may be viewed as coercive.

23.8 Corollary and Sub-studies

As with any other research, subject participation in corollary or sub-studies not essential to the primary aims of the research should be on a voluntary basis. This is particularly important when the primary research offers a potential benefit, such as treatment, that might compel the potential subject to agree to something that they otherwise would not.

HIPAA reinforces this ethical principle by explicitly stating that authorization for "unconditioned" activities, for which there is no associated treatment, benefit or other effect on the individual subject associated with participation, cannot be required. The published preamble to HIPAA Omnibus clarifies the basis for this position, and the requirement that authorization for unconditioned activities involve a clear opt-in mechanism, stating:

> "*This limitation on certain compound authorizations was intended to help ensure that individuals understand that they may decline the activity described in the unconditioned authorization yet still receive treatment or other benefits or services by agreeing to the conditioned authorization."* and *"an opt out option does not provide individuals with a clear ability to authorize the optional research activity, and may be viewed as coercive by individuals."*

As with authorization for future research, it is acceptable to combine in a single document the authorization for a conditioned activity, such as a clinical trial, with authorization for an unconditioned activity such as a corollary or sub-study that does not directly benefit or effect the individual participant, provided that:

1. The authorization clearly differentiates between the conditioned and unconditioned research activities;
2. The authorization clearly allows the individual the option to opt in to the unconditioned research activities; and
3. Sufficient information is provided for the individual to be able to make an informed choice about both the conditioned and unconditioned activities.

Separate authorization must be obtained for each research activity that involves the use and disclosure of psychotherapy notes. For example, authorization for the use and disclosure of psychotherapy notes for a clinical trial cannot be combined with an authorization for the use and disclosure of those psychotherapy notes for a corollary research activity.

23.9 De-identification of PHI under the Privacy Rule

Covered entities may use or disclose health information that is de-identified without restriction under the Privacy Rule. The "Safe Harbor" method permits a covered entity to de-identify data by removing all 18 data elements that could be used to identify the individual or the individual's

relatives, employers, or household members. The covered entity also must have no actual knowledge that the remaining information could be used alone or in combination with other information to identify individuals. Under this method, the identifiers that must be removed are the following:

1) Names.
2) All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP Code, and their equivalent geographical codes, except for the initial three digits of a ZIP Code if, according to the current publicly available data from the Bureau of the Census:
    a. The geographic unit formed by combining all ZIP Codes with the same three initial digits contains more than 20,000 people.
    b. The initial three digits of a ZIP Code for all such geographic units containing 20,000 or fewer people are changed to 000.
3) All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.
4) Telephone numbers.
5) Facsimile 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 resource locators (URLs).
15) Internet Protocol (IP) address numbers.
16) Biometric identifiers, including fingerprints and voiceprints.
17) Full-face photographic images and any comparable images.
18) Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification.

Alternatively, a qualified statistician may certify that the risk is very small that health information could be used, alone or in combination with other available information, to identify

individuals. The qualified statistician must document the methods and results of the analysis that justify such a determination. This analysis must be retained by the covered entity for 6 years from the date of its creation or when it was last acted on, whichever is later.

The Privacy Rule permits a covered entity to assign to, and retain with, the de-identified health information, a code or other means of record re-identification if that code is not derived from or related to the information about the individual and is not otherwise capable of being translated to identify the individual. The covered entity may not use or disclose the code or other means of record identification for any other purpose and may not disclose its method of re-identifying the information.

NOTE: Data that is considered de-identified under HIPAA may still be considered human subject data under the Common Rule, particularly when working with a small data set that can be further divided into smaller subsets. Additionally, while coded information may be de-identified under HIPAA, if the investigator holds or has the ability to access both the code and the data, the information is considered identifiable private information under the Common Rule.

23.10 Limited Data Sets and Data Use Agreements

Limited data sets are data sets stripped of certain direct identifiers. Limited data sets may be used or disclosed only for public health, research, or health care operations purposes. Because limited data sets may contain identifiable information, they are still PHI and as such are not considered de-identified under the Privacy Rule. Unlike de-identified data, protected health information in limited data sets may include: addresses other than street name or street address or post office boxes, all elements of dates (such as admission and discharge dates) and unique codes or identifiers not listed as direct identifiers. The following direct identifiers must be removed for PHI to qualify as a limited data set:

1) Names;
2) postal address information, other than town or city, state, and ZIP code;
3) telephone numbers;
4) fax numbers;
5) email addresses;
6) social security numbers;
7) medical record numbers;
8) health plan beneficiary numbers;
9) account numbers;
10) certificate or license numbers;
11) vehicle identifiers and license plate numbers;

12) device identifiers and serial numbers;

13) URLs;

14) IP addresses;

15) biometric identifiers; and

16) full-face photographs and any comparable images.

Before disclosing a limited data set, a covered entity must enter into a data use agreement (DUA) with the recipient, even when the recipient is a member of its workforce. The data use agreement establishes the parameters around the proposed uses and disclosures of the data, who is permitted to have access to the data, and stipulates that no other use will be made of the data, no attempt will be made to identify or contact individuals whose data are included in the limited data set, that appropriate safeguards are in place to protect the data from unauthorized use and that the recipient will report any uses or disclosures of the PHI that they become aware of that not in keeping with the terms of the DUA. Data Use Agreements for the purposes of research are available through the HRPP/IRB office. Data Use Agreements should be submitted to the IRB along with the other project materials so that HMH has a record of the agreement.

23.11 Research Subject Access to PHI

With few exceptions, the Privacy Rule guarantees individuals access to their medical records and other types of health information. One exception is during a clinical trial, when the subject's right of access can be suspended while the research is in progress. The subject must have been notified of and agreed to the temporary denial of access when providing consent and authorization. Any such notice must also inform the individual that the right to access will be restored upon conclusion of the clinical trial. Language accommodating this exclusion is included in the applicable HMH research consent/authorization templates.

23.12 Accounting of Disclosures

The Privacy Rule generally grants individuals the right to a written "Accounting of Disclosures" of their Protected Health Information made by a covered entity without the individual's authorization in the six years prior to their request for an Accounting. A covered entity must therefore keep records of such PHI disclosures for 6 years.

It is important to understand the difference between a use and a disclosure of PHI. In general, the use of PHI means communicating that information within the covered entity. A disclosure of PHI means communicating that information to a person or entity outside the covered entity. The Privacy Rule restricts both uses and disclosures of PHI, but it requires an accounting only for certain PHI disclosures.

Generally, an Accounting of Disclosures is required for:

1) Routinely Permitted Disclosures (e.g., under public health authority, to regulatory agencies, to persons with FDA-related responsibilities) with limited exceptions (e.g., law enforcement, national security, etc.)
2) Disclosures made pursuant to:
    a. Waiver of Authorization
    b. Research on Decedents' Information
    c. Reviews Preparatory to Research

An accounting is not needed when the PHI disclosure is made:

1) For treatment, payment, or health care operations.
2) Under an Authorization for the disclosure.
3) To an individual about himself or herself.
4) As part of a limited data set under a data use agreement.

The Privacy Rule allows three methods for accounting for research-related disclosures that are made without the individual's Authorization or other than a limited data set: (1) A standard approach, (2) a multiple-disclosures approach, and (3) an alternative for disclosures involving 50 or more individuals. Whatever approach is selected, the accounting is made in writing and provided to the requesting individual. Accounting reports to individuals may include results from more than one accounting method.

24 Information Security

HMH has established standards and safeguards to protect patient's information and to ensure compliance with federal and state information security regulations. It is the responsibility of investigators to familiarize themselves with and comply with these standards. The use of personal laptops, desktops, portable/USB drives, and other non-HMH devices for storage of research data is [discouraged/prohibited]. In the instances when a non-HMH computer or device must be used for the purposes of storing, even temporarily, or transmitting PHI or PII (Personally Identifiable Information) for research, the safeguards of the device must be verified by [Information Services] and a User Agreement completed. Additionally, any potential or known breach of a device or of research data must be immediately reported to both the IRB and Corporate Compliance so that appropriate steps can be taken to assess the situation, protect the information, and comply with regulations. Lost or stolen HMH devices must also be reported to Security.

Provisions for Data Security must be described in applications to the IRB and updated as necessary. When information containing direct identifiers such as Social Security numbers or PHI including data considered sensitive is to be transferred outside of the institution, the provisions for data security may be subject to further review and approval by the [Information Security Officer].

See the HMH's Policies on Patient Privacy and Information Security for further information.

25 Special Topics

25.1 Community Based Research

Community based research (CBR) is research that is conducted as an equal partnership between academic investigators and members of a community. In CBR projects, the community participates fully in all aspects of the research process. *Community* is often self-defined, but general categories of community include geographic community, a community of individuals with a common problem or issue, or a community of individuals with a common interest or goal.

Where research is being conducted in communities, investigators are encouraged to involve members of the community in the research process, including the design and implementation of research and the dissemination of results when appropriate. The Office of Research Administration will assist the investigator in developing such arrangements.

The most significant community involvement is in a subset of CBR called Community Based Participatory Research (CBPR) where there is an equal partnership between the academic investigators and members of a community, with the latter actively participating in all phases of the research process including the design and implementation of research and the dissemination of results when appropriate.

Questions to be considered as CBR studies are developed, and issues that the IRB will consider when reviewing CBR are as follows:

- How was the community involved or consulted in defining the need for the proposed research (i.e., getting the community's agreement to conduct the research)?
- How was the community involved or consulted in generating the study research plan?
- How will the research procedures, including recruitment strategies and consent processes be assessed to ensure sensitivity and appropriateness to various communities (e.g., literacy issues, language barriers, cultural sensitivities, etc.)?
- How will the community be involved in the conduct of the proposed research?
- How will community members who participate in the implementation of the research be trained and supervised?
- How have "power" relationships between investigators and community members on the research team, and in subject recruitment strategies been considered to minimize coercion and undue influence?
- What are the risks and benefits of the research for the community as a whole?
- How will boundaries between multiple roles (e.g., investigator, counselor, peer) be maintained, i.e., what happens when the investigator/research staff is the friend, peer, service provider, doctor, nurse, social worker, educator, funder, etc.)
- How will the research outcomes be disseminated to the community?

- Is there a partnership agreement or memorandum of understanding to be signed by HMH investigator and community partners that describes how they will work together?

When CBR studies are proposed, the above information will be included in the submission materials. When the IRB reviews CBR studies, it will include, either as members or consultants, individuals with expertise in community based research.

25.2 Transnational Research

The IRB will review all transnational research involving 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."

All policies and procedures that are applied to research conducted domestically should be applied to research conducted in other countries, as appropriate.

For transnational research, the HMH IRB seeks sufficient knowledge of the local research context by requesting approval for the project from local IRBs or ethics committees (which may or may not be OHRP-registered) and/or local letters of support. The source of this information will depend on the nature of the study, on the country and on the resources available to the investigator. Where there is a local IRB/IEC, HMH IRB must receive and review the foreign institution or site's IRB/IEC review and approval of each study prior to beginning the research at the foreign institution or site.

In some circumstances where research may be performed internationally and/or in settings where there are no IRBs, the HMH IRB may, prior to approval of the research, require additional verification and information from people outside the particular research project who are familiar with the customs, practices, or standards of care where the research will be taking place, such as local IRBs or ethics committees, other HMH investigators with knowledge of the region, or a consultant who is an expert on the region. These individuals may either provide a written review of a particular research plan or attend an IRB meeting to provide the HMH IRB with recommendations based on his or her expertise.

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 permit 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.

25.2.1.1 IRB Responsibilities

In addition to standard IRB review, the IRB will consider the following in the review of transnational research:

1. The investigator and research staff are qualified to conduct research in that country including knowledge of relevant laws, regulations, guidance and customs.
2. The consent process and consent documents are appropriate for the languages of the subjects and communication with the subject population. Arrangements are considered to communicate with the subjects throughout the study (e.g., to answer questions).
3. The IRB considers how modifications to the research will be handled. The IRB and investigators should consider as many contingencies (e.g., survey questions) as possible when research is reviewed and approved.
4. The IRB considers how complaints, non-compliance, protocol/research plan deviations and unanticipated problems involving risks to participants or other are handled.
5. The IRB considers how post-approval monitoring will be conducted.
6. The IRB considers if the investigator has obtained the appropriate host country permissions to conduct research (e.g., institutional, governmental or ministerial, IRB, local or tribal). When appropriate, the IRB communicates and coordinates with the local institutions or ethics committees.
7. The IRB considers mechanisms for communicating with the investigators and research staff when they are conducting the research in other countries.

25.2.1.2 Investigator Responsibilities

1. It is the responsibility of HMH investigator and the foreign institution or site to assure that the resources and facilities are appropriate for the nature of the research.
2. It is the responsibility of HMH investigator and the foreign institution or site to confirm the qualifications of the investigators and research staff for conducting research in that country(ies).
3. Investigators obtain all appropriate host country permissions to conduct research (e.g., institutional, governmental or ministerial, IRB, local or tribal).
4. It is the responsibility of HMH investigator and the foreign institution or site to ensure that the consent process and consent document are appropriate for the languages of the subjects and communication with the subject population. Arrangements are

considered to communicate with the subjects throughout the study (e.g., to answer questions).

5. It is the responsibility of HMH investigator and the foreign institution or site to ensure that the following activities will occur.
    a. Initial review, continuing review, and review of modification
    b. Post-approval monitoring
    c. Handling of complaints, non-compliance and unanticipated problems involving risk to subjects or others.
6. The IRB will not rely on a local ethics committee that does not have policies and procedures for the activities listed above.
7. Investigators will consider how complaints, non-compliance, protocol/research plan deviations and unanticipated problems involving risks to participants or other are communicated to the IRB.
8. It is the responsibility of HMH 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 to obtain consent of research participants, etc.).
9. Investigators cooperate with the IRB regarding how and when post-approval monitoring will be conducted.
10. Investigators consider mechanisms for communicating with the IRB when they are conducting the research in other countries.

25.2.1.3 Consent Documents

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. Verification of the back translation should be placed in the IRB file.

25.2.1.4 Monitoring of Approved Transnational 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.

When the IRB and a local ethics committee will both be involved in the review of research, there is a plan for coordination and communication with the local IRB/IECs.

The IRB will require documentation of regular correspondence between the HMH investigator and the foreign institution or site and may require verification from sources other than the HMH investigator that there have been no substantial changes in the research since its last review.

25.3 Research Repositories and Research Involving Coded Private Information or Biological Specimens

25.3.1 Biological Specimens

All activities involving the collection of human biological specimens for research purposes, as well as the research use of specimens collected for clinical care, must be conducted under the terms of an IRB approved research protocol. The collection and use of human biological specimens (either identifiable or de-identified) must comply with all applicable laws and regulations for research involving human biological specimens or superseding requirements.

25.3.2 Regulatory Oversight

Under HSS regulations, a human subject is a living individual about whom an investigator conducting research obtains

- data through intervention or interaction with the individual, or
- identifiable private information

Whether research involving biological specimens meets the definition of human subjects research is based on a) how the specimens were obtained and b) whether the specimens include identifiable private information.

If the specimens are obtained specifically for research purposes, then they have been collected through intervention or interaction with the individual and, thus, the research meets the definition of human subjects research. If the specimens were not collected for research purposes but as part of routine clinical care or other non-research purpose, then the research only meets the definition of human subjects research if the specimens include identifiable private information (See below for policies on coded specimens).

FDA regulations do not apply to biological specimens unless they are gathered as part of a clinical investigation involving human subjects or being used to test a medical device (See Section13 for more detail on FDA regulations). HIPPAA does not cover biological specimens but does cover protected health information (PHI) linked to the specimens (See Section 23 for more detail on HIPAA).

If the research meets the definition of human subjects research, then all of the requirements of this document apply.

25.3.3 IRB Review

Research involving only biological specimens may be exempt under Exemption Category #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." However, in order to qualify under this category, all of the specimens must exist prior to the research being submitted to the IRB.

Non-exempt research only involving biological specimens may be eligible for expedited review if it is minimal risk and falls within one of the following categories:

- (2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture [with restrictions]
- (3) Prospective collection of biological specimens for research purposes by noninvasive means.
- (5) Research involving materials… that have been collected, or will be collected solely for non-research purposes

All non-exempt research involving biological specimens that are not eligible for expedited review must be reviewed at a convened IRB meeting.

For all non-exempt research involving biological specimens, informed consent and documentation of consent is required unless waived by the IRB.

25.3.4 Coded Human Data or Biological Specimens

HMH IRB policy is based on the OHRP guidance document entitled, "Guidance on Research Involving Coded Private Information or Biological Specimens" (October 16, 2008 http://www.hhs.gov/ohrp/policy/cdebiol.html). This document:

1. 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).

2. Reaffirms OHRP policy that, under certain limited conditions, research involving **only** coded private information or specimens is not human subjects research.

3. Clarifies the distinction between (a) research involving coded private information or specimens that does not involve human subjects and (b) human subjects research that is exempt from the requirements of the HHS regulations.

4. References pertinent requirements of the HIPAA Privacy Rule that may be applicable to research involving coded private information or specimens.

Note: The FDA definition of human subjects differs from the Common Rule definition. Use of coded specimens for FDA-regulated research such as research on In Vitro Diagnostic Devices requires assessment according to the FDA regulations and guidelines. Investigators should contact the IRB office for guidance.

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

code exists, enabling linkage of the identifying information to the private information or specimens.

Guidance:

Obtaining identifiable private information or identifiable specimens for research purposes constitutes human subjects research. *Obtaining* identifiable private information or identifiable specimens includes, but is not limited to:

1. Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that have been provided to the investigator from any source; and

2. Using, studying, or analyzing for research purposes identifiable private information or identifiable specimens that were 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 per the Common Rule definition if both of the following conditions are 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:

    1. 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);

    2. 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

    3. 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)-(c) 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 subjects research is determined to be exempt (See Section 5), 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 11.9).

25.3.5 Who Should Determine Whether Coded Private Information or Specimens Constitutes Human Subjects Research

The investigator in consultation with the IRB Chair or Director of the IRB Office will determine if the research involving coded information or specimens requires IRB review. If the request is verbal (by phone or in person) or by email, it is the investigator's responsibility to maintain documentation of such a decision. If 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.

25.3.6 Data or Biological Sample Repositories

A repository is a collection of data or biological specimens whose organizers:

- Receive data or specimens from multiple sources
- Maintain the data or specimens over time
- Control access to and use of data or specimens by multiple individuals and/or for multiple purposes, which may evolve over time

These policies and procedures apply to both data and biological sample repositories. For simplicity, both will be referred to as samples in this document.

There are two type of repositories:

- Non-research repositories created and maintained for purposes that are totally unrelated to research. Such purposes may include diagnosis, treatment, billing, marketing, quality control, and public health surveillance.
- Research repositories created and maintained specifically for research purposes. Such purposes may include databases to identify prospective subjects, patient outcome information to evaluate treatment effectiveness, and tissues samples for future research

25.3.6.1 Non-research Repositories

Even though repositories were not created for research purposes, they may contain information that is of great interest to researchers. The creation (or operation) of non-research databases or repositories does not involve human subject research and does not require IRB oversight. However, IRB oversight is required for use in research of identifiable private information or identifiable human specimens from non-research databases and repositories (including data/tissue banks and registries).

- When research involves identifiable private information or identifiable human specimens each research use must receive prospective IRB review and approval and continuing IRB oversight
- Researchers should submit an application for IRB review and receive IRB approval before initiating the research.
- Where available, the application should include any available information about the circumstances under which the information or specimens were originally collected.
- Investigators who believe their research may be exempt from the human subject regulations should include a request for exemption #4 with the IRB application.
- The IRB may require researchers to obtain the informed consent of subjects for research involving information or specimens contained in non-research databases or repositories. The IRB can waive the requirement for informed consent if the research meets the criteria in the regulation

25.3.6.2 Research Repositories

Research repositories involve three components:

- the collectors of samples;
- the storage and data management center; and
- the recipient investigators.

Sample collection

If the samples were collected for research purposes or are associated with information that can identify the donor, then Informed consent must be obtained from the donor unless appropriately waived by the IRB.

Informed Consent information should include:

- A clear description of
  - the operation of the database;
  - the specific types of research to be conducted;
  - the conditions under which data will be released to recipient-investigators; and

    - procedures for protecting the privacy of subjects and maintaining the confidentiality of data
- A statement regarding future withdrawal of the data from the study (i.e., state whether subjects may, in the future, request that their data be destroyed or that all personal identifiers be removed from data).
- Other information, such as the length of time that data will be stored, subjects' access to information learned from the research, and secondary uses of the samples should be considered as appropriate.

Repositories should have data submission policies to ensure that the data was collected in an ethical manner, such as informed consent and IRB approval.

Sample Storage and Management

Repositories should have written policies on:

- Data and tissue submission requirements
    - Informed consent
    - IRB review
- Physical and procedural mechanisms for the secure receipt, storage, and transmission of information and specimens
- Policies on release of information and specimens
    - Coding
    - Release of identifier
    - Certificates of Confidentiality

Recipient Investigators

Recipient-investigators should have a written data use agreement with the repository. The data use agreement should specify under what conditions the data is being released to the recipient-investigator(s). The terms under which the data is released determine whether the research requires IRB oversight.

25.3.6.3 IRB Oversight

Operation of a research repository and its data management center under the auspices of HMH is subject to oversight by the HMH IRB. Proposals to establish a repository must be submitted to the IRB, specifying the conditions under which data and specimens may be accepted and shared, and ensuring adequate provisions to protect the privacy of subjects and maintain the confidentiality of data. The IRB also reviews and approves a sample collection protocol and informed consent document for distribution to sample collectors and their local IRBs.

25.3.6.4 HIPAA

PHI in non-research repositories may not be used or disclosed for research purposes without written authorization or an IRB waiver of authorization or use of information that does not require authorization (e.g., de-identification).

HIPAA applies to submission of PHI to a research repository and authorization is required when appropriate. HIPAA does not allow authorization for unspecified future use. Under HIPAA, PHI can be stored and used for research purposes if:

- The research is limited to the purpose stipulated in the authorization
- New authorization is obtained if the PHI is to be released for a new use
- The IRB grants a waiver of authorization
- The PHI is only being used for research that does not require an authorization

25.4 Certificate of Confidentiality (CoC)

Certificates of Confidentiality are issued by the National Institutes of Health (NIH) 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. A CoC does not protect against voluntary disclosures by the investigator, but those disclosures must be specified in the informed consent form. An investigator may not use the Certificate to withhold data if the participant consents in writing to the disclosure.

Generally, any research project that collects personally identifiable, sensitive information and that has been approved by an IRB operating under either an approved Federal-Wide Assurance issued by OHRP or the approval of the FDA is eligible for a Certificate. Federal funding is not a prerequisite for a NIH-issued Certificate, but the subject matter of the study must fall within a mission area of the National Institutes of Health, including its Institutes, Centers and the National Library of Medicine.

25.4.1 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."

25.4.2 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 investigators and institutions from being compelled to disclose information that would identify research subjects, CoCs 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 CoC. Research can be considered "sensitive" if it involves the collection of:

1. Research on HIV, AIDS, and STDs;
2. Information about sexual attitudes, preferences, practices;
3. Information about personal use of alcohol, drugs, or other addictive products;
4. Information about illegal conduct;
5. Information that could damage an individual's financial standing, employability, or reputation within the community;
6. Information in a subject's medical record that could lead to social stigmatization or discrimination; or
7. Information about a subject's psychological well-being or mental health.
8. Genetic studies, including those that collect and store biological samples for future use;
9. Research on behavioral interventions and epidemiologic studies.

This list is not exhaustive. Investigators contemplating research on a topic that might qualify as sensitive should contact the IRB Office for help in applying for a certificate.

In the consent process and form, investigators should tell research subjects that a CoC 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 CoC is in effect.

25.4.3 Limitations

The protection offered by a Certificate of Confidentiality is not absolute. A CoC protects research subjects only from legally compelled disclosure of their identity. It does **not** restrict voluntary disclosures by subjects or investigators.

For example, a CoC does not prevent investigators 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 investigators intend to make such disclosures, this should be clearly stated in the consent process and the 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

1. The subject (or, if he or she is legally incompetent, his or her legal guardian) consents, in writing, to the disclosure of such information;
2. Authorized personnel of the Department of Health and Human Services (DHHS) request such information for audit or program evaluation, or for investigation of DHHS grantees or contractors and their employees; or
3. Release of such information is required by the federal Food, Drug, and Cosmetic Act or regulations implementing that Act.

25.4.4 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 funding research in a scientific area similar to the project.

If the research is conducting a sensitive research project that is covered by the Agency for Healthcare Research and Quality (AHRQ) confidentiality statute (42 U.S.C. section299a-1(c) entitled “Limitation on Use of Certain Information”) or the Department of Justice (DoJ) confidentiality statute (42USC section 3789g), then a CoC is not required.

If there is an Investigational New Drug Application (IND) or an Investigational Device 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).

25.5 Mandatory Reporting

While any person may make a report if they have reasonable cause to believe that a child or elder was abused or neglected, New Jersey law mandates that certain persons who suspect child or elder abuse or neglect report this to the Division of Child Protection and Permanency or Adult Protective Services .

HMH policy requires the solicitation of informed consent from all adult research subjects and, where appropriate, assent from children involved as research subjects, in addition to the permission of their parents. In situations where conditions of abuse or neglect might be

revealed, mandated reporters should make themselves known as such to parents of children under age 18, to subjects who are children, and to subjects who are potential victims of abuse or neglect.

Investigators should consult these sources to determine if potential subjects should be advised of mandatory reporting requirements during the informed consent process.

25.6 HMH Students and Employees as Subjects

When HMH students and/or employees are being recruited as potential subjects, investigators must ensure that there are additional safeguards for these subjects. The voluntary nature of their participation must be primary and without undue influence on their decision. Investigators must emphasize to subjects that neither their academic status or grades, or their employment, will be affected by their participation decision.

To minimize coercion, investigators must avoid, whenever possible, the use of their students and employees in procedures which are neither therapeutic nor diagnostic. In these latter situations, investigators must solicit subjects through means such as bulletin board notices, flyers, advertisements in newspapers, and announcements in classes or laboratories other than their own. When entering a classroom to recruit students and conduct research, e.g., administer a survey, investigators must do so at the end of the class period to allow non-participating students the option of leaving the classroom, thereby alleviating pressure to participate.

25.7 Student Research

25.7.1 Human Subject Research and Course Projects

Learning how to conduct ethical human subject research is an important part of a student's educational experience. Research activities that are designed as part of a course requirement for purposes of learning experience only and are **not "**designed to develop or contribute to generalizable knowledge" **may** not require IRB review and approval if all of the following conditions are true:

- Results of the research are viewed only by the course instructor for teaching purposes and discussed within the classroom for teaching and learning purposes.
- Results of the research are not made public through presentation (outside of the classroom) and are not published in paper or electronic format (e.g., cannot be made available on the internet, cannot be published in a journal, etc.).
- Research procedures are no more than minimal risk.
- Vulnerable populations are not targeted (e.g., children under age 18, prisoners, persons who are cognitively impaired, etc.).
- Data collected are recorded in such a manner that the subjects are not identifiable (images in videotapes and photographs and voices on audiotape are identifiable).
- When appropriate, an informed consent process is in place.

25.7.1.1 **Responsibility of the Course Instructor:**

The course instructor is responsible for communicating to the students the ethics of human subject research, for ensuring the protection of human subjects (including a process is in place for obtaining voluntary informed consent from research subjects when appropriate), and for monitoring the students' progress.

When designing a project, students should be instructed on the ethical conduct of research and on the preparation of the IRB application when such is required. In particular, instructors and students should:

- Understand the elements of informed consent;
- Develop appropriate consent documents;
- Plan appropriate strategies for recruiting subjects;
- Identify and minimize potential risks to subjects;
- Assess the risk-benefit ratio for the project;
- Establish and maintain strict guidelines for protecting privacy and confidentiality, and
- Allow sufficient time for IRB review (if necessary) and completion of the project.

In making a determination of whether or not a class research project requires IRB review, the instructor is encouraged to contact the IRB office for assistance.

25.7.1.2 Individual Research Projects Conducted by Students

Independent study projects, senior theses, undergraduate research projects, Masters and advanced degree research, and similar exercises must be independently submitted for IRB review. It is important to keep in mind that any human subject research activity that will ultimately contribute to part or all of a thesis, dissertation, or other type of publication or presentation must go through the IRB review process prior to enrolling subjects and collecting data. IRB review/approval cannot occur after a study has begun.

Students and advisors should contact the IRB Office with any questions.

25.7.2 Independent Study, Theses and Dissertations

These research activities are considered to meet the federal definition of human subject research and must be independently submitted to the IRB by the student-investigator. However, when students conduct research as part of a course of study, a faculty member ultimately is responsible for the protection of the subjects, even if the student is the primary investigator and actually directs the project. Advisers assume the responsibility for students engaged in independent research, and instructors are responsible for research that is conducted as part of a course. It is expected the institution granting the degree has reviewed the study and agrees the study has merit to proceed. Documentation of a review by the advisor of the study will be required.

Students may not serve as principal investigators. They must have a faculty sponsor who fulfills the principal investigator eligibility criteria and who will serve as principal investigator and faculty advisor on the study.

25.8 Genetic Studies

Genetic research studies may create special risks to human subjects and their relatives. These involve medical, psychosocial, legal 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?

25.9 Case Reports Requiring IRB Review

In general, an anecdotal report on one or 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 does 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 is considered research and would require IRB approval.

25.9.1 Definitions

Single Case Report. The external reporting (e.g., publication, poster or oral 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, poster or oral 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.

25.10 Research supported by the Department of Defense (DoD)

Research supported by the Department of Defense (DoD) is reviewed and conducted in compliance with part 219 of title 32 CFR, part 980 of title 10 USC, applicable parts of title 21 CFR (50, 56, 312, 600, 812), DoD Directive 3216.02, DoD Directive 3210.07, and applicable additional requirements from respective DoD component(s).

A. Application and Scope

The following additional requirements apply to all biomedical and social/behavioral research involving human research participants conducted under the jurisdiction of HMH when it:

- Conducts, reviews, approves, oversees, supports manages or otherwise is contractually subject to regulation by the DoD; and/or
- Human subject research performed under the jurisdiction of UMMC using DoD property, facilities, or assets.

In most cases, protocols covered by these requirements also will have review, approval and oversight by the DoD Human Research Protections Program.

HMH assures that DoD supported research complies with all relevant DoD human subjects protection requirements, including but not limited to:

- The Belmont Report
- Title 32 Code of Federal Regulations Part 219 (32 CFR 219), Department of Defense Regulations, “Protection of Human Subjects” (DoD adoption of the “Common Rule”)

- Title 45 Code of Federal Regulations Part 46, (45 CFR 46) Department of Health and Human Services Regulations, "Protection of Human Subjects," Subparts B, C, and D as made applicable by DoD Directive (DoDD) 3216.02
- Title 21 Code of Federal Regulations 50, 56, 312, and 812, Food and Drug Administration (FDA) Regulations
- DoDD 3216.02, "Protection of Human Subjects and Adherence to Ethical Standards in DoD-supported Research"
- Title 10 United States Code Section 980 (10 USC 980), "Limitation on Use of Humans as Experimental Subjects"
- DoDD 3210.7, "Research Integrity and Misconduct"
- DoDD 6200.2, "Use of Investigational New Drugs in Force Health Protection"

B. Key Additional Requirements Not Covered by Title 45 CFR 46, Subparts B, C and D; 21 CFR 50, 56, 312, and 812

1. Minimal Risk – [DODD 316.02, enclosure 3, para 6b]

The definition of minimal risk based on the phrase "ordinarily encountered in daily life or during the performance of routine physical or physiological examination 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 work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain.)

2. Undue Influence – [DoDD 3216.2, enclosure 3, para 7e1]

Service members shall follow their command policies regarding the requirement to obtain command permission to participate in research involving human subjects while on-duty and for approving off-duty employment or activities. Superiors (e.g., military and civilian supervisors, unit officers, and noncommissioned officers (NCOs)) are prohibited from influencing the decisions of their subordinates (e.g., junior enlisted personnel and equivalent civilians) regarding participation as subjects in research involving human subjects. Unit officers and senior NCOs in the chain of command shall not be present at the time of research subject solicitation and consent during any research recruitment sessions in which members of units under their command are afforded the opportunity to participate as research subjects. When applicable, officers and NCOs so excluded shall be afforded the opportunity to participate as research subjects in a separate recruitment session. During recruitment briefings to a unit where a percentage of the unit is being recruited to participate as a group, an ombudsman not connected in any way with the proposed research or the unit shall be present to monitor that the voluntary nature of individual participants is adequately stressed and that the information provided about the research is adequate and accurate.

3. Education and Training – [DoDD 3216.2, enclosure 3, para 5]

For initial and continuing research ethics education for all personnel who conduct, review, approve, oversee, support, or manage human participant research, there may be specific DoD educational requirements or certification required. The IRB shall use this guidance document as the basis for reviewing any DoD supported research and shall ensure that the PI has received this document before approving the research. The DoD component may evaluate the education policies to ensure the personnel are qualified to perform the research, based on the complexity and risk of the research.

4. Appointment of a Research Monitor – [DODD 3216.02, enclosure 3, para 8]

- The IRB considers the appointment of a research monitor:
    - Required for research involving greater than minimal risk, although the IRB or organizational official can require this for a portion of the research or studies involving no more than minimal risk if appropriate.
    - The research monitor is appointed by name and shall be independent of the team conducting the research.
    - There may be more than one research monitor (e.g. if different skills or experience are needed.
    - The monitor may be an ombudsman or a member of the data safety monitoring board. The IRB must approve a written summary of the monitors' duties, authorities, and responsibilities.
    - The IRB or HRPP official shall communication with research monitors to confirm their duties, authorities, and responsibilities.
    - The duties of the research monitor are determined on the basis of specific risks or concerns about the research.
        - May perform oversight functions (e.g. observe recruitment, enrollment procedures, and the consent process, oversee study interventions and interactions, review monitoring plans and unanticipated problems involving risks to participants or others, oversee data matching, data collection and analysis).
        - May discuss the research protocol with researchers, interview human subjects, and consult with others outside of the study.
        - Report observations and findings to the IRB or a designated official.
- The research monitor has the authority to:
        - Stop a research study in progress.
        - Remove individuals from study.
        - Take any steps to protect the safety and well-being of participants until the IRB can assess.

5. ***Additional protections for pregnant women, prisoners, and children (Subparts B, C and D) of 45 CFR 46) – [DODD 3216.02, enclosure 3 para 7]***

- Research involving pregnant women, prisoners, and children are subject to the DHHS Subparts B, C. and D.

- 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.
- 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.
- Research involving a detainee as a human participants is prohibited.

- Research involving prisoners cannot be reviewed by the expedited procedure.
- When the IRB reviews research involving prisoners, at least one prisoner representative must be present for quorum.
- 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.

- When a prisoner becomes a participant, if the researcher asserts to the IRB that it is in the best interest of the prisoner-participant to continue to participate in the research while a prisoner, the IRB Chair may determine that the prisoner-participant may continue to participate until the convened IRB can review this request to approve a change in the research protocol and until the organizational official and 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 a 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.

6. ***Limitation of Waivers and Exceptions from Informed Consent - [DODD 3216.02, enclosure 3 para 13; 10 U.S.C. 980]***

If the research participant meets the definition of "experimental subject," policies and procedure prohibit a waiver of the consent process unless a waiver is obtained from the Assistant Secretary of Defense for Research and Engineering. The Assistant Secretary of Defense for Research and Engineering may waive the requirements for consent when all of the following are met:

- The research is necessarily to advance the development of a medical product for the Military Services.
- The research may directly benefit the individual experimental subject.
- The research is conducted in compliance with all other applicable laws and regulations.

Research involving a human being as an experimental subject is an activity, for research purposes, where there is an intervention or interaction with a human being for the primary purpose of obtaining data regarding the effect of the intervention or interaction. If the research participant does not meet the definition of "experimental subject," policies and procedure allow the IRB to waive the consent process.

For classified research, waivers of consent are prohibited.

7. ***Limitations on Compensation for U.S. Military Personnel - [DODD 3216.02, enclosure 3 para 11, Dual Compensation Act and 24 U.S.C. 30]***

The Dual Compensation Act prohibits an individual from receiving pay from more than one position for more than an aggregate of 40 hours of work in one calendar week. This prohibition applies to employees paid from either appropriated or non-appropriated funds, or a combination thereof, and includes temporary, part-time and intermittent appointments. This law if not applicable to enlisted off-duty military personnel in relation to their military duty.

When research involves U.S. military personnel, limitations on dual compensation include:

- Federal employees while on duty and non-Federal persons may be compensated for blood draws for research up to $50 for each blood draw.
- 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.
- Prohibit an individual from receiving pay of compensation for research during duty hours.
- U.S. military personnel may be compensated for research if the participant is involved in the research when not on duty.

8. ***Requirement for Reporting - DODD 3216.02, enclosure 3 para 4(b)(4)***

The Institution shall promptly (no longer than within 30 days) notify the HRPO of the following: when significant changes to the research protocol are approved by the IRB, the results of the IRB continuing review, if the IRB used to review and approve the research changes to a different IRB, when the institution is notified by any Federal department or agency or national organization that any part of its HRPP is under investigation for cause involving a DoD-supported research protocol, and all UPIRTSOs, suspensions, terminations, and serious or continuing noncompliance regarding DoD-supported research involving human subjects.

9. ***Recordkeeping Requirements - [DoDD 3216.2, enclosure 3 para 15)]***

DOD regulations require all institutions engaged in DoD-conducted or -supported research involving human subjects to retain records for at least 3 years after the completion of the research. The DoD Components may rely on the non-DoD institutions to keep the required records that were generated by the institution, or the DoD Components may make arrangements to transfer the records.
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.

10. ***Addressing and Reporting Allegations of Non-Compliance with Human Research Protections - [DoDD 3216.2 enclosure 3 para 16]***

All findings of serious or continuing noncompliance that have been substantiated by inquiry or investigation shall be reported to the Assistant Secretary of Defense for Research and Engineering in a timely manner.

11. ***Prohibition of Research with Prisoners of War (POW) and Detainees - [DoDD 3216.2, , enclosure 3 para 7(c)]***

Research involving a detainee, as defined in DoD Directive 2310.01E, as a human subject is prohibited.

This prohibition does not apply to activities covered by investigational new drug or investigational device provisions of DOD regulations when for the purpose of diagnosis or treatment of a medical condition in a patient. Such treatment (e.g., an investigational new drug) may be offered to detainees with the detainees' informed consent when the medical products are subject to DOD regulations as investigational new drugs or investigational medical devices, and only when the same product would be offered to members of the U.S. Military Services in the same location for the same medical condition and only when consistent with established medical practice involving investigational drugs and devices. Such permitted treatment involving detainees as subjects shall comply with applicable DOD regulations.

12. ***Classified research [DODD 3216.02, enclosure 3 para 13]***

The involvement of classified information may be limited to information needed for IRB approval and oversight of the research; information needed to inform the human subjects during the consent process; and information provided by the human subjects during the course of the research. Secretary of Defense approval is required for all classified non-exempt research involving human subjects.

Informed consent procedures shall include:
(1) Identification of the Department of Defense as the supporting institution of the research, unless the research involves no more than minimal risk. The Secretary of Defense may grant an exception to this requirement on the grounds that providing this information could compromise intelligence sources or methods.
(2) A statement that the research involving human subjects is classified and an explanation of the impact of the classification.

The IRB shall determine whether potential human subjects need access to classified information to make a valid, informed consent decision.

IRB review shall be conducted using a full board review. Use of an expedited review procedure is prohibited.

13. Additional Requirements for DoD Sponsored Research

a) New research and substantive scientific amendments to approved research shall undergo scientific review and the review is considered by the IRB. The IRB may rely on outside experts to provide an evaluation of scientific merit.
b) When conducting research with international populations, additional safeguards for research conducted with international populations include: The Organization or Researcher has permission to conduct research in that country by certification or local ethics review and the Researcher follows all local laws, regulations, customs, and practices.
c) Disclosure regarding the provisions for research-related injury follow the requirements of the DoD component.
d) Surveys performed on Department of Defense personnel must be submitted, reviewed, and approved by the Department of Defense after the research protocol is reviewed and approved by the IRB.
e) When conducting multi-site research, a formal agreement between organizations is required to specify the roles and responsibilities of each party.
f) The following shall be promptly (no longer than within 30 days) reported to the DoD human research protection officer:
    a. When significant changes to the research protocol are approved by the IRB.
    b. The results of the IRB continuing review.
    c. Change of reviewing IRB.

d. When the organization is notified by any Federal department, agency or national organization that any part of the HRPP is under investigation for cause involving a DoD-supported research protocol.

g) If consent is to be obtained from the research participant's LAR, the research must intend to benefit the individual participant. The determination that research is intended to be beneficial to the individual research participant must be made by the IRB.

h) An exception from consent in emergency medicine research is prohibited unless a waiver is obtained from the Secretary of Defense.

C. Responsibilities

It is the responsibility of the principal investigator to ensure compliance with all additional Department of Defense (DoD) requirements for human subject protection. It also is the responsibility of the IRB to ensure that all additional requirements by Department of Defense components for human subject protection have been met before IRB approval of the research project.