



MaineHealth  
Standard Operating Procedures  
Human Research Protection Program/Institutional Review Board

**Pre-2018 Common Rule  
For Studies initially approved on or before January 20, 2019**

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# **1 Human Research Protection Program**

Maine Medical Center (MaineHealth) fosters a research environment that promotes respect for the rights and welfare of individuals recruited for, or participating in, research conducted by or under the auspices of the Organization. In support of this, MaineHealth has established a Human Research Protection Program (HRPP). The MaineHealth HRPP, in partnership with its research community, is responsible for ensuring the ethical and equitable treatment of all human subjects in research conducted under MaineHealth’s auspices.

## **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;
- Provide timely and high-quality education, review, and oversight of human research projects; and
- Facilitate excellence in the conduct of human subjects research.

The HRPP includes mechanisms to:

- Monitor, evaluate, and continually improve the protection of human research participants
- Exercise responsible oversight of human subjects research;
- Educate IRB members, investigators, and 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**

MaineHealth Human Research Protection Program operates under the authority of the Institutional Human Research Protection Program (HRPP) Policy. 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 MaineHealth.” The HRPP Policy and these operating procedures are made available to all MaineHealth investigators and research staff and are posted on the Office of Research Compliance website (<http://mmcri.org>).

### 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:** 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 Subjects Research.** Human Subjects 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 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 FDA under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), or need not meet the requirements for prior submission to the FDA under these sections of the FD&C Act, but the results of which are intended to be later submitted to, or held for inspection by, the FDA 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 FDA under section 505(i) of the FD&C 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 FDA under section 520(g) of the FD&C 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 obtains data through intervention or interaction with the individual or through identifiable private information [[45 CFR 46.102\(f\)](#)].

- **Intervention** means both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
- **Interaction** means communication or interpersonal contact between investigator and subject.
- **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).
- **Identifiable** information means information that is individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information).

**Human Subject (FDA):** 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 either a healthy individual or a patient. For research involving medical devices, a human subject is also an 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\(i\)](#)]

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

1. **[Human drugs](#)** – 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). The primary intended use of a drug product is achieved through chemical action or by being metabolized by the body.
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."

3. **Biological Products** - include a wide range of products such as vaccines, blood and blood components, allergens, 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.
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. **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

MaineHealth 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 26), MaineHealth 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. These principles are:

1. **Respect for Persons**, which involves the acknowledgment and support of autonomy, and protection of those with diminished autonomy
2. **Beneficence**, which involves ensuring that possible benefits of research are maximized, and possible harms are minimized
3. **Justice**, which involves the fair distribution of the benefits and burdens of research through the equitable selection of subjects

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

#### 1.5 Regulatory Compliance

The HRPP facilitates compliance with federal regulations, state and local law and organizational policies. Human subjects research at MaineHealth is conducted in accordance with applicable regulations and requirements including, but not limited to, the following:

Research conducted, supported, or otherwise subject to regulation by any federal department or agency which adopts the [Common Rule](#) is reviewed and conducted in accordance with the Common Rule. 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.

Research subject to **FDA regulations** is reviewed and conducted in accordance with applicable regulations including, but not limited to, [21 CFR 50](#), [21 CFR 56](#), [21 CFR 312](#) and [21 CFR 812](#).

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 supported by the **Department of Defense (DoD)** is reviewed and conducted in compliance with [32 CFR 219](#), [10 USC 980](#), 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 28.6 for additional information pertaining to compliance with DoD-funded research.

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

The revised Common Rule establishes that all studies approved, waived under .101(i), or determined exempt before January 21, 2019 will be subject to the old rule through the close of study. All protocols approved or determined exempt on or after January 21, 2019 will be subject to the new rule. At this time, MaineHealth will not be transitioning individual studies approved or exempted under the old rule to all applicable provisions of the new rule.

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

MaineHealth voluntarily commits to follow the guidelines for investigators outlined in the International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines (sometimes referred to as ICH-GCP or E6) for the conduct of clinical trials when required by a sponsor or funding agency. MaineHealth applies the ICH-GCP guidelines for investigators only to the extent that they are compatible with FDA, DHHS, and other applicable regulations. At this time, industry-sponsored clinical trials of drugs are reviewed by external IRBs; as such, the IRB of record for a protocol subject to ICH-GCP E6 is responsible for the relevant ICH-GCP IRB guidelines.

### 1.7 Federalwide Assurance (FWA) and IRB Registration

The federal regulations require that federally-funded human subjects 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 subjects research conducted at that site complies with federal regulations pertaining to the protection of human subjects.

In its FWA, MaineHealth has opted to limit the application of the FWA to non-exempt human subjects research conducted or supported by DHHS or federal agencies that have adopted the Common Rule.

When human subjects research is not subject to the Common Rule or FDA regulations, MaineHealth ensures that human research subjects benefit from equivalent protections by applying the Common Rule standards, with purposeful deviations that do not meaningfully diminish protections as noted within this manual.

Likewise, federal regulations require IRBs to register with DHHS if they will review human subjects research conducted or supported by DHHS or research subject to FDA regulations.

The [HHS registration system database](#) can be used to verify the status of MaineHealth’s FWA, IORG, and IRB registration.

MaineHealth’s Federal Registration Numbers	
FWA	00003993
IORG	0000154
IRB Registration	00000262

## 1.8 Research Under the Auspices of MaineHealth

Research under the auspices of MaineHealth includes research conducted at or using any property or facility of MaineHealth, conducted by or under the direction of any employee or agent of MaineHealth (including students, residents, fellows) in connection with his or her MaineHealth position or responsibilities, or involving the use of MaineHealth's non-public information (e.g., medical records) to identify, contact, or study human subjects. The research may be externally funded, funded from internal sources, or conducted without direct funding.

All human subjects research under the auspices of MaineHealth or its affiliates is under the jurisdiction of the MaineHealth HRPP. Human subjects research that MaineHealth is engaged in (per OHRP or FDA guidelines) is under the jurisdiction of the MaineHealth IRB, unless MaineHealth chooses to rely upon another IRB for review and ongoing IRB oversight of the research (the IRB of record for the research).

**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."* 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 MaineHealth facilities or by MaineHealth Principal or Sub-Investigators (as defined on the FDA 1572 or equivalent, or the delegation of responsibilities log) requires review by an MaineHealth- designated IRB. Exceptions to this requirement may be granted on a case-by-case basis (e.g., when MaineHealth's] involvement in the research is limited to the provision of a common diagnostic procedure and associated reading or analysis).

When external organizations and researchers wish to conduct research that is under the auspices of MaineHealth, the external organization or researchers must consult with the MaineHealth HRPP or IRB staff prior to initiating any research activities at or involving MaineHealth.

Members of the Office of Research Compliance, at the direction of the HRPP Director, IRB Chair, and Vice Chair, with the assistance legal counsel as needed, are authorized to determine whether

MaineHealth is engaged in a particular research study. Investigators and other institutions **may not** independently determine whether MaineHealth is engaged in a particular research study.

When MaineHealth 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 engagement please refer to OHRP's [Guidance on Engagement on Institutions in Human Subjects Research](#).

## **1.9 Written Procedures**

These Standard Operating Procedures (SOPs) for Human Research Protection detail the procedures, standards, and requirements for research with human subjects under the auspices of MaineHealth and the requirements of the MaineHealth IRB. This is not a static document. The SOPs are reviewed annually and may be revised by the Office of Research Compliance (ORC) Director with input from ORC staff, Counsel, Institutional Official and others as necessary.

The MaineHealth HRPP will keep the 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, through email, and other forums. These SOPs will be available on the MaineHealth HRPP website. Changes to the SOPs are communicated to investigators, research staff, IRB members, and IRB staff by way of e-mail communication and posting on the ORC website.

## **1.10 MaineHealth HRPP Structure**

The HRPP consists of individuals, departments, and committees with responsibilities for human research protections such as, the Institutional Official, ORC Director, IRB Manager and ORC Staff, the IRB, the Research Financial Conflict of Interest Committee, Research Pharmacy, Legal Counsel, investigators, research staff, Grants and Contracts, Clinical Trials Office, the Institutional Biosafety Committee (IBC), the Radiation Safety Committee (RSC), and others. 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 program. The IO is legally authorized to represent MaineHealth. The IO is the signatory of the FWA and assumes the obligations of the FWA. At MaineHealth, The Director of the Maine Medical Center Research Institute and Vice President for Research is the Institutional Official. The IO is responsible for ensuring that the MaineHealth HRPP and IRB(s) have the resources and support necessary to fulfill their responsibilities and to comply with the regulations and requirements that govern human subject research. Such resources include, but are not limited to:

- Staffing commensurate with the size and meeting space, complexity of the research program;

- Appropriate office space, meeting 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 noncompliance;
- Access to legal counsel; and
- Ensuring that the IRB, investigators, and staff receive training related to human research protections.

At a minimum of annually, the IO reviews HRPP and IRB functions, requirements, and resources and makes adjustments as needed.

The IO is also responsible for:

- Fostering, supporting and maintaining a culture that supports the ethical conduct of research involving human subjects and compliance with applicable regulatory and other requirements;
- 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 human subjects research under the auspices of MaineHealth;
- Providing training and educational opportunities for IRB members and staff to support their ability to review research in accordance with ethical standards and applicable regulations;
- Providing training and educational opportunities for investigators and research staff to support their ability to conduct research in accordance with ethical standards and applicable regulations; and
- Taking action as necessary to ensure the protection of human subjects and compliance with regulatory and other requirements.

The IO has the authority to suspend, terminate, or disapprove research or take other actions, such as sanctions or restrictions of research privileges or uses of research data, as necessary, to ensure the proper conduct of research, the protection of human subjects, the autonomy and authority of the IRB, compliance with regulatory and other requirements, or to protect the interests of MaineHealth. However, the IO may not approve research that has been disapproved (or not yet approved) by the IRB.

The IO must complete either the OHRP Human Subject Assurance Training, or the CITI Training Module for IOs. The ORC will support the continuing education of the IO by providing information and updates on topics related to human research protections.

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

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. The Senior Director, Research Administration assists the IO in the above responsibilities. However, the IO is ultimately responsible and is expected to be knowledgeable about human subject protections and research at the organization.

### **1.10.2 Director of the Office of Research Compliance (ORC)**

The Office of Research Compliance is comprised of two human research divisions (IRB Administration, and SEQuR; Support of Education and Quality Improvement for Researchers), as well as the Institutional Animal Care and Use Committee (IACUC). The IRB reports to the Director of ORC, who reports to the Senior Director, Research Administration. The director, working in close partnership with the IRB Manager, is responsible for:

- Developing, managing and evaluating policies and procedures that ensure compliance with state, and federal regulations and MaineHealth policies. This includes monitoring changes in regulations and policies that relate to human research protection and overseeing the administration of the IRB;
- Advising the IO on key matters regarding human subjects research;
- Implementing the organization’s HRPP SOPs;
- Overseeing the administration of the HRPP, including the supervision of staff;
- Overseeing the administration of IRB Reliance Agreements and Independent Investigator Agreements;
- Submitting, implementing and maintaining an approved FWA through the IO and the Department of Health and Human Services Office of Human Research Protection (OHRP);
- Managing the finances of the MaineHealth HRPP and IRB;
- Developing and implementing needed improvements and ensuring follow-up of actions, as appropriate, for the purpose of managing risk in the research program;
- Developing training requirements as required and as appropriate for IRB members, investigators, and staff, and ensuring that training is completed on a timely basis;
- Serving as the primary contact at MaineHealth for the Office for Human Research Protections (OHRP) of the U.S. Department of Health and Human Services, the FDA, and other regulatory agencies on matters of human research protections; and
- Serving as a liaison to the RCOI Committee to ensure oversight of the research COI program as it pertains to the review of human subjects research.

### **1.10.3 IRB Manager**

The IRB Manager reports to the ORC Director, and has primary responsibility for:

- Administration of the IRB

- Supervision of the Research Compliance Coordinators (RCCs)
- Assisting the IRB in its efforts to review research and ensure the protection of human subjects;
- Assisting investigators in their efforts to carry out the organization's research mission;
- Serving as an internal expert resource for questions and other matters regarding the protection of human subjects.

#### **1.10.4 ORC Staff**

In addition to the leadership structure described above, the staffing for the ORC includes Research Compliance Coordinators (RCCs) responsible for IRB Administration, and Research Education and Compliance Officers (RECOs) who staff the SEQuR. ORC staff for MaineHealth 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 RCC staff report to the IRB Manager, and the RECOs report to the ORC Director.

#### **1.10.5 Institutional Review Board (IRB)**

MaineHealth has one internal IRB, appointed by the Institutional Official (IO). The IRB prospectively reviews and makes decisions concerning all non-exempt human subjects research under the auspices of MaineHealth unless it has been determined that MaineHealth is not engaged in the research or MaineHealth has entered into agreement with an external IRB to serve as the IRB of record. The IRB is responsible for the protection of the rights and welfare of human research subjects, 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.

The IRB functions independently of, but in coordination with, other organizational committees and officials. The IRB, however, makes independent determinations whether to approve, require modification in, or disapprove research based upon whether 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.

MaineHealth also uses the services of external IRBs including WIRB, NCI CIRB Adult and Pediatric IRBs, and others. External IRBs are primarily relied upon for the review and oversight of industry initiated/industry funded clinical trials. MaineHealth may enter into reliance agreements for other reasons, for example, when required as a term or condition of a grant.

### 1.10.6 Legal Counsel

The MaineHealth HRPP relies on the Organization's Legal Counsel or designee for the interpretation of state law and the laws of other jurisdictions where research is conducted as they apply to human subjects research. Counsel is available to provide guidance on other relevant topics as needed.

### 1.10.7 Department Chairs

Department Chairs are responsible for ensuring that the investigator is qualified by training and experience to conduct the proposed research.

Department chairs/leaders are required to review all proposals before they are submitted to the IRB for review. The signature of the Department chair indicates that the investigator is qualified and has the necessary credentials and resources to safely conduct the study, and (2) attests to the scientific validity of the study, meaning that:

- The research uses procedures consistent with sound research design; and
- The research design is sound enough to reasonably expect the research to yield the expected knowledge.

### 1.10.8 Principal Investigators

The Principal Investigator (PI) is ultimately responsible for the protection of the human subjects participating in research they conduct or oversee. The PI is expected to abide by the highest ethical standards when developing a research plan and to incorporate the principles of the [Belmont Report](#). The PI is expected to conduct research in accordance with the IRB approved research plan and to personally conduct or oversee all aspects of the research. In addition to complying with all applicable regulatory policies and standards, PIs must comply with organizational and administrative requirements for conducting research. The PI is responsible for ensuring that all investigators and research staff complete all organization required trainings as well as training for their specific responsibilities in any given research study. When investigational drugs or devices are used, the PI is responsible for ensuring an appropriate plan for their storage, security, dispensing, accounting, and disposal.

The IRB reviews investigator qualifications when reviewing research and may determine that an investigator may not serve as PI or may require the addition of other investigators to supplement the expertise available on the research team or to conduct or oversee certain aspects of the research.

The PI for human subjects research under the auspices of MaineHealth must be a non-trainee (e.g., attending, etc.). Waivers to this requirement will be considered by the IO or designee, on a case by case basis. Factors to be considered in granting the waiver include past human research experience, past experience as a PI at other organizations etc.

Individuals who are debarred, disqualified, or otherwise restricted from participation in research or as a recipient of grant funds for research by a federal, state, or other agency **may not** serve as PI.

Individuals with a history of compliance issues related to the conduct of research (e.g., recipients of a FDA Warning Letter) will be considered on a case-by-case basis. Factors to consider include whether corrective actions have been accepted as adequate, whether information from an audit or quality review indicates that the issues have been resolved, and similar considerations.

### **1.10.9 Other Related Units**

#### **1.10.9.1 Grants and Contracts**

The Grants and Contracts staff review all research agreements with grantors and sponsors including federal, foundation, industry, and non-profit. This review ensures that all terms of the award (grant or contract) are in compliance with organizational policies. Only designated senior individuals within Grants and Contracts have the authority to approve funding proposals and to execute research agreements on behalf of the organization. The Authorized Organizational Representative signs all contracts and agreements on the recommendation of senior Grants and Contracts staff.

Grants and Contracts ensures that required AAHRPP language (see Section 24) is included in contracts. The Contracts Officer, and the Medical Coverage Analyst (MCA) have access to the contract and the consent documents to confirm they are consistent in terms of costs to subjects and who pays in case of injury. The IRB office, in consultation with the Contracts Officer, coordinates efforts to ensure that all applicable individuals have filed appropriate COI disclosures to meet investigator COI policies.

Grants and Contracts ensures that all senior/key personnel on federal grant applications have disclosed financial interests within the 12 months prior to submission. If a financial conflict is identified, the grants and contracts office reports such conflict to the federal awarding agency and ensures no funds are spent prior to managing the conflict.

When the grant or contract agreement includes human research activities that will be conducted by investigators who are not employees or agents of MaineHealth, a subcontract is executed between MaineHealth 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 MaineHealth.

#### **1.10.9.2 MaineHealth Pharmacy**

MaineHealth Pharmacy is responsible for storing, accounting for, dispensing, and compounding of most investigational drugs used in research, whether conducted with inpatient or outpatients. The manufacture/compounding of drug products not commercially available is coordinated by MaineHealth pharmacy. Waivers from use of the MaineHealth pharmacy for handling investigational drugs will be considered on a case by case basis by the MaineHealth Pharmacy.

The Pharmacy is available to provide guidance to investigators in relation to the management of the study drugs.

### **1.10.10 Study-Specific Coordination**

In addition to IRB approval, PIs 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 areas and committees, including, but not limited to:

- Pathology/laboratory
- Pharmacy
- Radiology
- Nursing
- Facilities where research activities will occur
- Departmental approvals
- Records access permissions (e.g., Epic etc.)
- Institutional Biosafety Committee
- Radiation Safety Committee
- Radioactive Drug Research Committee

When applicable, either electronic signature, or e-mail confirmation of support, collaboration, permission, or approval from the designated authority, will be included in the appropriate IRBNet package for the study. The submission will be reviewed in the ORC to ensure that all necessary sign-offs are included. The IRB reserves the right to request review by or consultation with any of the above listed or other organizational committees or components even when such review or consultation is not required by policy.

If the research sites, or research personnel, are also under the jurisdiction of another IRB, documentation of the external IRB's approval or agreement to cede or waive review is required.

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

## **2 Quality Assurance**

MaineHealth 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**

The ORC should be notified in advance, whenever possible, of upcoming external audits or inspections/monitoring of research whether the study is reviewed by the MaineHealth IRB or an external IRB on MaineHealth's behalf. HRPP representatives may participate in entrance and exit interviews and otherwise observe or support the audit or inspection. Likewise, MaineHealth representatives may assist in the development of any responses to audits or inspections.

All reports from external monitors, auditors, or inspectors must be submitted to the SEQuR Office for review. The RECO will review such reports to monitor for issues that could impact the rights or welfare of human subjects and for issues indicative of possible serious or continuing noncompliance. If such issues are identified, the ORC will initiate the process for noncompliance as identified in Section 19. The SEQuR Office will conduct further investigation or training as necessary.

When MaineHealth is engaged in research reviewed by an external IRB, all reports from audits or inspections must be submitted to ORC for review. Corrective and preventative actions (CAPA), a follow up review, or other actions may be required to ensure the protection of human subjects and to support compliance.

### **2.2 Investigator Compliance Reviews**

The Support of Education and Quality Improvement for Researchers (SEQuR) Office is a division of the ORC. The SEQuR Office or, on occasion, other internal or external staff, conduct post-approval directed (for cause) and routine (not for cause) compliance reviews of human subjects research conducted under the auspices of MaineHealth. Additionally, the IRB 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 MaineHealth policies, to identify areas for improvement, and to provide recommendations based on existing policies and procedures. As appropriate, the results of compliance reviews will be reported to the ORC Director, IRB Manager, the MaineHealth IRB (when the MaineHealth IRB is the IRB of record), the investigator, and other MaineHealth leadership, as appropriate.

If it is identified during the course of a review that subjects in a research project may have been exposed to unexpected serious harm or risk of harm, the reviewer will promptly report such findings to the ORC Director and the IRB Manager. The study team will be responsible for reporting such findings to the IRB of Record.

If issues are identified that indicate possible misconduct in research, the procedures in the Responding to Allegations of Scientific or Other Scholarly Misconduct Policy will be initiated.

Compliance reviews may include:

- Requesting progress reports from investigators
- Examining investigator-held research records and records held by pharmacy or other ancillary services
- Reviewing source documentation
- Reviewing the recruitment process and materials
- Reviewing consent materials and the documentation of consent
- Observing the consent process and other research activities
- Verifying HIPAA authorization
- Interviewing investigators and research staff
- Interviewing research subjects
- Reviewing projects to verify from sources other than the investigator that no unapproved changes have occurred since previous review
- Conducting other monitoring or auditing activities as deemed appropriate by the HRPP or IRB.

### **2.3 IRB Compliance Reviews**

The SEQuR Office of the ORC, or, on occasion, other internal or external staff, 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.

Review activities may include:

- Review of the IRB minutes to evaluate whether adequate documentation of the meeting discussion and any required determinations has occurred, and that quorum was met and maintained
- Reviewing IRB files to evaluate whether adequate documentation of exemptions, expedited review, and other outside of committee reviews has occurred
- Reviewing consent forms to evaluate whether all required elements are included
- Reviewing IRBNet Reports to evaluate whether all required fields are completed accurately
- Verifying IRB approvals for external sites or investigators
- Reviewing metrics (for example, time from submission to first review) to evaluate the quality, efficiency, and effectiveness of the IRB review process
- Reviewing the workload of the IRB and IRB staff

- Other review activities as appropriate

The ORC Director, IRB Manager, and IRB Chair will review the results of IRB compliance reviews with the IRB at a minimum of once annually. If substantive deficiencies are identified in the review, a corrective action plan will be developed by the IRB Chairs and the ORC Director and approved by the IO. The ORC Director will have responsibility for implementing and reporting progress on the corrective action plan, the results of which will be evaluated by the IO.

## **2.4 HRPP Quality Assessment and Improvement**

Not less than annually, a meeting is held by the ORC Director and IRB Manager in consultation with others as needed to establish a quality assessment/ improvement (QA/QI) plan to assess the compliance, and the quality, efficiency, and effectiveness, of the HRPP. The plan will include, at a minimum, the following:

- The goals of the plan with respect to achieving and maintaining compliance
  - At least one objective to achieve or maintain compliance
  - At least one measure of compliance
  - The methods to assess compliance and make improvements
- The goals of the plan with respect to achieving targeted levels of quality, efficiency, and effectiveness
  - At least one objective of quality, efficiency, or effectiveness
  - At least one measure of quality, efficiency, or effectiveness
  - The methods to assess quality, efficiency, or effectiveness and make improvements.

The ORC Director will meet regularly throughout the year with the staff responsible for performing the assessments called for in the plan to review progress and to identify opportunities for improvement. As required, the ORC Director, IRB Manager, IO, and Senior Director of Research Administration will evaluate whether the respective goals were achieved and determine if any additional actions or monitoring are necessary. If at any time substantive or concerning issues or trends are identified, the ORC Director will report those issues or trends to the appropriate parties (e.g., the IO, the IRB Chair, SEQuR) and, if appropriate, propose a CAPA plan.

The SEQuR Office is responsible for tracking internal data and metrics that are informative when considering HRPP and IRB efficiency, effectiveness, workload, and resources. Metrics reports will be provided to the ORC Director, IRB Manager, and IRB Chair at least annually.

### **3 Education & Training**

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

MaineHealth recognizes that a vital component of a comprehensive human research protection program is an education program. MaineHealth is committed to providing training and on-going education for IRB members and the staff of the HRPP and IRB, 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 the IRB Manager and others as applicable for an orientation session. At the session, IRB processes, regulations, and resources will be reviewed. The new member will receive copies of, or links to, the following and other relevant information:

- Belmont Report
- These standard operating procedures
- Federal regulations relevant to the IRB
- Tools used by IRB reviewers (checklists etc.)
- IRB Meeting Schedule
- Contact Information for the ORC, IRB Manager, and the ORC Director

##### **Initial Education**

IRB members and ORC and IRB staff must complete the required modules in the biomedical CITI Course in the Protection of Human Research Subjects or other training determined to be equivalent by the IRB Manager, in consultation with the ORC Director. IRB members must complete the CITI Good Clinical Practice (GCP) course as well.

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

##### **Continuing Education**

To ensure that oversight of human research is ethically grounded, and the decisions made by the IRB are consistent with current regulatory and policy requirements, training is continuous for IRB members throughout their service on the IRB.

In addition to CITI training, MaineHealth may also use the following activities as a means for offering continuing education to IRB members and ORC and IRB staff:

- In-service training at IRB meetings
- Training workshops
- Webinars

- Email distribution of articles, announcements, presentations, and other materials relevant to human subject protections

IRB members and HRPP and IRB staff are also required to complete CITI basic or refresher training every 3 years or other training determined to be equivalent by the ORC Director.

The activities for continuing education vary on a yearly basis depending on areas of need, as determined by the IRB Manager and ORC Director. Whenever possible, the HRPP provides support for staff and IRB members to attend PRIM&R, OHRP, and other relevant conferences.

The ORC determines minimum attendance requirements for continuing education and tracks participation. Fulfillment of training requirements is included as part of the evaluation of the performance of IRB members, alternates, and staff. Continuing failure to complete training may result in a member's service being discontinued or not renewed.

### **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 with human subject responsibilities. MaineHealth is committed to providing training and on-going education for investigators and research staff members on human subject protections and other relevant topics.

#### **3.2.1 Initial Education**

Investigators and research staff who interact or intervene with subjects, or who use subjects' identifiable information for the purposes of research, must complete MaineHealth's CITI Courses relevant to the type of research being conducted and the investigator or staff member's responsibilities. Additional information detailing MaineHealth's CITI training requirements is available [www.mmcri.org](http://www.mmcri.org).

Evidence of current training (date of completion within 3 years of application date) for each member of the research team is confirmed by ORC staff. Applications and additions of study personnel will not be approved unless all study team members are current in training.

#### **Waiver of Initial Education**

Individuals who can provide documentation verifying that they have successfully completed human subject research training equivalent to that required by the MaineHealth may request a waiver of MaineHealth's specific training requirements. ORC Staff will review the documentation and determine if it satisfies organizational standards.

#### **3.2.2 Continuing Education**

Initial training is considered current for a period of three years by which time investigators and research staff must complete basic or refresher CITI training or provide evidence of equivalent training as described above. There is no exception to this requirement.

Training will be verified at the time of continuing review and with applications to add study personnel. If training has not been completed or has lapsed and is not completed in a timely manner, the

investigator or staff member may be removed from the study or otherwise restricted from participating in the research.

In addition to the basic requirements described above, MaineHealth will periodically provide training on topics relevant to human subject protections, regulations, policies and standards, and IRB submission processes and requirements. Training may be provided via in-service, workshops, webinars, e-Learning, or through the distribution of articles, presentations, and other materials. Investigators and staff may request training or offer training suggestions by contacting the ORC.

## 4 “Human Subjects” and “Research” Determinations

Some MaineHealth activities involve systematic investigations, but may not be generalizable (e.g., quality improvement, program evaluations, classroom research activities), and some activities result in generalizable findings, but were not conducted as systematic investigations (e.g., case studies). None of these activities are research.

The responsibility for initial determination whether an activity constitutes “research” rests with the individual with primary responsibility for the activity. This individual should make this determination based on the definitions of “[research](#)” and “[clinical investigation](#)” as provided by the Common Rule and FDA regulations, respectively. Consultation with the ORC is encouraged. Because the analysis can be complex, individuals with any questions regarding the applicability of the regulations to their activities are urged to request a determination that an activity does or does not involve research. Such requests should be submitted via the completion of a “Human Subjects Research Determination” application in IRBNet.

Similarly, the responsibility for the initial determination of whether research involves “human subjects” rests with the investigator. Under the Common Rule, information is considered identifiable, and thus involving human subjects, when the identity of the subject is or may be readily ascertained by the investigator or associated with the information. It should be noted that this definition differs significantly from [de-identified in accordance with HIPAA standards](#). FDA regulations do not incorporate the concept of “identifiability” in the evaluation of whether an activity is a clinical investigation (or research) subject to FDA regulations. For example, the use of de-identified human specimens to evaluate the safety or effectiveness of a diagnostic device is considered human subjects research subject to FDA regulations. Investigators are urged to submit for a determination whenever they are uncertain if a research study involves “human subjects” as defined by the Common Rule or FDA. Such requests should be submitted via the completion of a MaineHealth Smartform Wizard along with the “Human Subjects Research Determination” application in IRBNet.

Investigators **may not** self-determine that research involving the use of **coded** private information or specimens does not involve “human subjects”. Such determinations should only be made by ORC staff using the process described above. An exception to this policy occurs when:

- the research is not subject to FDA regulations AND
- the coded private information or specimens are to be obtained from an MaineHealth IRB-approved repository AND
- the rules of that repository forbid the release of identifiable information, the key or code that would enable re-identification, or the release of sufficient information that investigators could readily ascertain the identity of subjects.

Human Subjects Research Determinations must be submitted, and determined, prospectively (i.e., before the proposed activity or research begins). Conducting human subjects research without IRB approval or exemption is noncompliance and will be managed as described in Section 19.

Determinations whether an activity constitutes human subject research will be made by ORC staff, in consultation with others as necessary according to the definitions in Section 1.3, applicable federal

regulations, and federal guidance. A determination letter will be issued and uploaded as a board document in IRBNet to document the determination. Investigators conducting research under the auspices of MaineHealth **may not** rely upon determinations made by other organizations or through the use of electronic (or other) determination tools.

## 5 Exempt Determinations

All research using human subjects must be approved by MaineHealth. Although certain categories of human subject research are exempt from IRB oversight, at MaineHealth the determination of exempt status must be made by ORC staff. MaineHealth may also choose to accept an exempt determination made by an external IRB, MaineHealth will consider such requests on a case by case basis.

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.

Exemptions are determined or granted, rather than approved. Exempt studies are exempt from the requirements of the [Common Rule](#) (i.e., 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.).

### 5.1 Limitations on Exemptions

The following limitations are applied to exemptions, regardless of funding source:

**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, or if the research is not federally funded and meets criteria for MaineHealth Flex Category Exemption 2a.

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

### 5.2 Exempt Research

With the above-referenced limitations, *and any other limitations or restrictions due to applicable law, regulation, or agency policy*, research activities not regulated by the FDA (see Section 5.4 for FDA Exemptions) in which the only involvement of human subjects is determined to be in one or more of the following categories may be determined exempt from IRB approval:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as
  - (i) research on regular and special education instructional strategies, or
  - (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
  - (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and

- (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation.
- 3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under category 2, if:
  - (i) the human subjects are elected or appointed public officials or candidates for public office; or
  - (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
- 4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

**NOTE:** To be eligible for this exemption, all of the materials must already be in existence at the time the research is proposed for an exempt determination.

- 5. Research and demonstration projects which are conducted by or subject to the approval of federal department or agency heads, and which are designed to study, evaluate, or otherwise examine:
  - (i) Public benefit or service programs;
  - (ii) Procedures for obtaining benefits or services under those programs;
  - (iii) Possible changes in or alternatives to those programs or procedures; or
  - (iv) Possible changes in methods or levels of payment for benefits or services under those programs.

The program under study must deliver a public benefit (e.g., financial or medical benefits as provided under the Social Security Act) or service (e.g., social, supportive, or nutrition services as provided under the Older Americans Act).

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

- 6. Taste and food quality evaluation and consumer acceptance studies,
  - (i) If wholesome foods without additives are consumed; or
  - (ii) If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the

level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

### **5.3 Flexibility**

With the above-referenced limitations, the MaineHealth ORC will follow the exemption categories at 45 CFR 46. Research activities not regulated by the FDA (see section 5.4 for FDA Exemptions) may also be reviewed and granted Exempt status based on the MaineHealth Flexibility Policy, the terms of which allow an appropriate level of flexibility for research involving no greater than minimal risk.

MaineHealth has developed exempt categories not found in the federal regulations, for projects that do not directly conform to a specific exempt category according to 45 CFR 46. These projects will be reviewed using an approval process identical to that used for exempt research categories 1-6 under 45 CFR 46.101(b).

MaineHealth Exemption 2a: Minimal risk research that involves a non-invasive intervention followed by data collection via survey, interview (including focus groups), or observation, unless: (i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation. Research that is federally funded, FDA-regulated or was issued a Certificate of Confidentiality is not eligible for this category. Research involving children is eligible for this category.

MaineHealth Exemption 7: Research in which study activity is limited to analysis of identifiable data existing at the time the research is proposed or that will be collected in the future for non-research purposes. For purposes of this research study, all research subject interactions and interventions have been completed and the data continues to contain subject identifiers or links. Research that is federally funded, FDA-regulated or was issued a Certificate of Confidentiality is not eligible for this category.

### **5.4 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\(c\)](#)]

See Section 17.7.1.2 and 17.7.2.3 for detailed discussion of this exemption for investigational drugs and devices (respectively).

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\(d\)](#)]

## 5.5 Procedures for Exemption Determination

To request an exempt determination, investigators submit the following materials in IRBNet:

### Required:

1. A completed **Exemption Request** form;
2. The MaineHealth Smartform Wizard;
3. Departmental Review Sign-Off

### As Applicable:

1. Information Sheets (i.e. information to be provided to participants to obtain prospective agreement as applicable) with the following points addressed:
  - a. A statement that the activities involve research
  - b. A description of the procedures to be performed
  - c. A statement that participation is voluntary
  - d. The investigator's name and contact information
  - e. For Category 3 research that involves subject deception: A statement that subjects will be unaware of or misled regarding the nature or purposes of the research
  - f. Patient Reimbursement Information (if applicable)
2. Subject materials (questionnaires, diaries, interview scripts/guides, data collection forms, surveys, etc.
3. Recruitment materials
4. HIPAA Forms (applicable only if the research activity involves seeing, using or disclosing protected health information- PHI)
  - Authorization to Use and Disclose PHI
  - HIPAA Request for Waiver or Alteration of Authorization
  - HIPAA Certification Form-Deidentification (This form is typically used for retrospective chart review for which none of the 'HIPAA identifiers' are recorded)
  - HIPAA Certification Form- Limited Data Set (LDS; with requirement for a Data Use Agreement if the LDS is proposed to be disclosed outside of Maine Health)
  - HIPAA Research on Decedents Request
5. Internal Services Sign-off
6. Letter(s) of permission from any non-MaineHealth sites; or, when applicable, documentation of IRB approval or exemption from the external site;

7. The Grant Application (if the project is federally-funded and MaineHealth is the IRB or serving as the IRB of record for the prime awardee)
8. When Tufts students are the subjects in a research study, a Letter of Support from the Dean

The ORC staff reviews all requests for exemptions and determines whether the request meets the criteria for exempt research. The reviewer's determination is documented on the **Exemption Determination Checklist** and uploaded into IRBNet. If the request does not appear to meet the definition of human subject research, the reviewer evaluates the proposal as described in Section 4.

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.

The exempt application, review documentation, and determination letter are maintained in the same manner and for the same length of time as other IRB review documentation.

Exempt determinations will include a termination date, with the maximum time allotted being 6 years. 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 it still qualifies for exemption.

Investigators must report any proposed additions to study personnel so that CITI training can be verified, and COI evaluated prior to their involvement with the research. Proposed modifications to the research itself must be submitted for a determination of whether the research still qualifies for exemption. Finally, investigators must submit a closure report when an exempt research project is complete so that the organization can maintain an accurate database of research activities.

## 6 Multi-site and Collaborative Research

When engaged in multi-site research, research involving external collaborators, or research that is otherwise under the jurisdiction of more than one IRB, MaineHealth acknowledges that each organization is responsible for safeguarding the rights and welfare of human subjects and for complying with applicable federal regulations. MaineHealth may choose to review the research in its entirety, only those components of the research MaineHealth is engaged in, rely on the review of another qualified IRB, or make other arrangements for avoiding duplication of effort. When MaineHealth is the prime awardee on a HHS grant, it will ensure that at least one IRB reviews the research in its entirety (**see section 9 regarding the single IRB requirement for multicenter grants awarded from NIH, where all sites are conducting all research procedures**).

When relying upon another IRB or when serving as the reviewing IRB for an outside organization or external investigator, a formal relationship must be established between MaineHealth and the outside organization or investigator through an IRB Authorization Agreement, Investigator Agreement, a Memorandum of Understanding, or other such written agreement. The written agreement must be executed before MaineHealth will accept any human research proposals from the outside organization or investigator or rely on the review of an external IRB.

IRB reliance agreements establish the authorities, roles, and responsibilities of the reviewing IRB and the relying organization. The procedures for reliance, including for communication, information-sharing, and reports, may be outlined in the reliance agreement or in companion SOPs or other materials. ORC staff utilize a checklist to ensure that reliance agreements and any accompanying materials address all requirements and are consistent with MaineHealth's standards. To support compliance, MaineHealth will make every effort to ensure as much consistency as possible across reliance agreements.

MaineHealth has signed the SMART IRB joinder agreement. When the organizations participating in the research are signatories to the joinder agreement, IRB reliance may be requested and documented utilizing the [SMART IRB](#) online reliance platform. MaineHealth will determine on a study-by-study basis whether the SMART IRB SOPs or alternative procedures will be utilized to implement the reliance via a reliance arrangement agreed upon between the relying and reviewing sites.

Requests for MaineHealth to either rely upon an external IRB or to serve as the IRB of record for an external organization or investigator should be submitted as early as possible in the grant/contract process by submitting a reliance request following the instructions in Section 8 of these SOPs.

See Section 8 for procedures and considerations involved in IRB reliance arrangements.

## 7 Research Previously Approved by Another IRB

When an investigator transfers research to MaineHealth that was previously approved by another IRB, the investigator must either submit a reliance request for MaineHealth to rely upon the current IRB of record, or submit the research for de novo review under MaineHealth procedures covered by these SOPs. No research activity may take place under MaineHealth auspices without the appropriate reliance, or IRB review and approval.

For research transfers where stopping research interventions or procedures 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 MaineHealth IRB approval is obtained.

## 8 IRB Reliance Arrangements in Multi-Site Research

MaineHealth investigators involved in multi-site research are encouraged to discuss with collaborators the possibility of shared IRB review, i.e., having one IRB review on behalf of all sites.

If the research is part of a multicenter grant awarded from NIH, single IRB (sIRB) review is required under most circumstances (<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-094.html>). The reader is referred to Section 9 for details specific to compliance with the NIH sIRB policy.

Investigators should contact ORC early in the multi-site grant/contract process to discuss possible sIRB options as discussed in 8.2 (MaineHealth Serving as the Reviewing IRB) and 8.3 (MaineHealth Ceding Review to an External IRB) below.

### 8.1 Reliance Agreements

Reliance agreements must be in place for all ceded IRB review arrangements. ORC ensures that these agreements are negotiated to reflect study-specific, respective responsibilities of the reviewing IRB and the relying Institutions. The Reliance Agreement:

- Documents the respective authorities, roles, responsibilities, and communication between an organization providing the ethical review and a participating organization relying on a reviewing IRB.
- Describes the responsibilities of all parties and how communication between parties will occur, for example, notifications of the outcome of regulatory review and management of federally-mandated reports such as reports of unanticipated problems, serious or continuing noncompliance, and suspensions or terminations of IRB approval.
- When IRB certification requirements apply (e.g., for NIH Genomic Data Sharing etc.), the agreement or written procedures will indicate who is responsible for meeting the certification requirements.
- Specifies contact information and personnel for both the sIRB and relying institution(s).

- Addresses whether the replying organization applies its FWA to some or all research, and ensure that the IRB review is consistent with requirements in the relying organization's FWA.
- Addresses which organization is responsible for obtaining any additional approvals from DHHS when the research involves Subpart B, C, or D determinations, or any applicable federal agency or department (e.g., DOD, etc.).

The institution that is awarded the funding for the research is responsible for maintaining all agreements and for ensuring that adequate and appropriate communication channels between the sIRB and participating sites are in place. Participating sites are responsible for maintaining copies of the site agreement in accordance with the terms of their FWA.

## **8.2 MaineHealth Serving as the Reviewing IRB**

### **8.2.1 Factors Considered by ORC to have MaineHealth provide IRB Services**

ORC Staff evaluate the following factors, and others as appropriate, when considering a request for an MaineHealth IRB to serve as the IRB of record for a particular study or studies:

1. The terms of the external site(s) FWA;
2. The accreditation status of the external site(s)
3. Prior experience with the site(s) and investigators;
4. The compliance history of the site(s) and investigators (e.g., outcomes of prior audits or inspections, corrective actions);
5. The research activities to be conducted at the external site(s);
6. The willingness of the external site(s) to accept MaineHealth's reliance terms and procedures; and/or
7. The ability of the site(s) to collaboratively provide meaningful oversight of the proposed research, taking into account factors such as:
  - a. The risks and procedures of the research;
  - b. The resources available at each site and ability to accommodate or collaborate with each other in observing the consent process, performing compliance reviews, investigations of potential noncompliance, and similar matters;
  - c. The expertise and experience of the MaineHealth IRB with the proposed research, subject population, and applicable regulations;
  - d. The ability of the MaineHealth IRB to comply with the relevant local context considerations of the external site(s), as provided by that site(s); and/or
  - e. The willingness or ability of the external site(s) to provide information and respond to questions regarding investigator qualifications, conflicts of interest, organizational requirements, local context, and other matters that may inform the IRB review.

The ORC staff member will present relevant factors for consideration by the Director of ORC (in consultation with the IO, as applicable) who will make the final decision regarding whether or not the MaineHealth IRB will serve as the reviewing IRB. The PI will be notified of the decision.

## **8.2.2 Responsibilities when MaineHealth is the Reviewing IRB**

### **8.2.2.1 Responsibilities of the MaineHealth IRB**

- Policies and procedures in the conduct of review for all sites (MaineHealth and external) will mirror those outlined throughout these SOPs, as set forth in Domain II of the AAHRPP accreditation standards. Possible exceptions are noted in 8.4 below. Additionally, the following MaineHealth IRB responsibilities are to be applicable for all sites:
  - Have the final authority to decide whether MaineHealth or external researcher or research staffs' COI and its management, if any, allows the research to be approved
  - Have the authority to request or conduct an audit of research being reviewed.
  - Make relevant IRB policies readily available to relying external sites, including their HRPP staff, researchers, and research staff, and ensure that changes to those policies are communicated as well.
  - Ensure that a MaineHealth ORC contact person along with contact information is specified for researchers and research staff to obtain answers to questions, express concerns, and convey suggestions regarding the MaineHealth IRB.
- Adding sites to an already approved IRB study will be considered a modification, and will be conducted by the expedited or full board process. In order for the review to be conducted via the expedited process criteria, such a modification is usually considered a "minor change to previously approved research'. Factors that will indicate that a full review is required may include, e.g., involvement of investigators with FCOI, FDA 483 issues that have not been resolved adequately, or any other site-specific issues that are deemed questionable. Additional site amendments (regardless of type of review) do not change the expiration date of the IRB approval for the 'main' protocol.

### **8.2.2.2 Responsibilities of the MaineHealth Principal Investigator**

- Submission of a plan for review to the IRB to ensure that the PI's at collaborating sites have access to current information regarding study status and current protocols, consent documents, etc. regarding the study. (Alternatively, the IRB can review the plan provided by the MaineHealth PI to ensure open communication with the collaborating site(s)).
- Coordinate with ORC to ensure submission to the IRB information pertaining to the particular characteristics of each site's local research context to be considered either (a) through knowledge of its local research context by the IRB, (b) through consultants, or (c) through review by appropriate designated institutional officials at external site(s). Additionally, the submission will also include details for the IRB's evaluation regarding the management plan for information that is relevant to the protection of participants (e.g., unanticipated problems involving risks to participants or others, Interim results, protocol modifications). When the MaineHealth researcher is the lead researcher of a multi-site study, this information will also be made known to the IRB of record (e.g., Independent IRB, etc.).

## **8.3 MaineHealth Ceding IRB Review to an External IRB**

### **8.3.1 Standing Reliance Agreements**

MaineHealth has standing agreements in place for the review of specific categories of research to engage the services of external IRBs including:

- WIRB
- NCI's Adult CIRB for NCI research involving adult subjects
- NCI's Pediatric CIRB for NCI research involving children
- Quorum
- Advarra

MaineHealth is a participating institution in the SMART IRB initiative as well, having signed an overarching agreement indicating willingness to cede to other institutions' IRBs, pending satisfactory evaluation of factors identified below.

Research that falls within the above parameters must be registered with MaineHealth prior to submission to the external IRB following the procedures outlined below. Post-approval requirements for investigators are also summarized below.

### **8.3.2 Factors Considered by ORC in the decision to allow MaineHealth to Cede to an External IRB**

MaineHealth may choose to enter into an agreement to rely upon other external IRBs, most commonly when required as a condition of a grant or contract. An ORC staff member evaluates the following factors, and others as appropriate, when considering a request to rely upon an external IRB:

1. The accreditation status of the proposed IRB;
2. The compliance history of the IRB (e.g., outcomes of prior audits or inspections, corrective actions);
3. Prior experience with the IRB;
4. The federal IRB registration and organizational FWA, as applicable;
5. The expertise and experience of the proposed IRB (e.g., with reviewing the type of research, research procedures, and subject population(s));
6. The research activities to be conducted at MaineHealth;
7. The risks and complexities of the proposed research;
8. The proposed reliance terms and procedures, including acceptance of MaineHealth local context issues, as well as the procedures for collaborative management of matters such as conflicts of interest processes, investigator training, noncompliance, unanticipated problems, and federal reports;
9. The plan for review and allowance of the incorporation of site-specific consent language; and
10. The plan for incorporation of other relevant local requirements or context information in the review process.

The ORC Staff member will present relevant factors for consideration to the ORC Director or designee (in consultation with the IO as applicable) who will make the final decision regarding whether or not to cede to the requested External IRB. The PI will be notified of the decision.

### **8.3.3 MaineHealth, External IRB, and MaineHealth Investigator Responsibilities When MaineHealth Cedes Review**

**8.3.3.1 The External IRB** has the same authority as the MaineHealth IRB and all determinations and requirements of the external IRBs are equally binding. See section 8.4 for possible exceptions to external IRB vs. MaineHealth responsibilities.

**8.3.3.2 MaineHealth** remains responsible for the conduct of the research in which it engages. Research reviewed by external IRBs remains subject to review, approval, oversight, and monitoring by MaineHealth (in cooperation with the reviewing IRB when appropriate) and must adhere to all applicable policies, procedures, and requirements of MaineHealth's HRPP. As with MaineHealth IRB-reviewed research, officials of MaineHealth may not approve research that is subject to a reliance agreement if it has not been approved by the reviewing IRB. See section 8.4 for possible exceptions to external IRB vs. MaineHealth responsibilities. ORC is responsible for notifying the reviewing IRB when MaineHealth policies that may impact IRB review are updated.

#### **8.3.3.3 Responsibilities of the MaineHealth Investigator When Using an External IRB**

- **General Compliance Requirement:**
  - The MaineHealth Investigator must be familiar with, and comply with the external IRB's policies and procedures for initial and continuing review, record keeping, prompt reporting, and any additional requirements or procedures outlined in the IRB reliance agreement or companion materials (e.g., reliance SOPs). All information requested by the reviewing IRB must be provided in a timely manner. MaineHealth will support investigator compliance with the terms of reliance agreements by providing investigators with a Reliance Arrangement Form that provides information relevant to their responsibilities.
  - Expectations of PI compliance, as detailed in these SOPs, remain in place regardless of the reviewing IRB.
  - Even though the External IRB may be reviewing the study, it must not commence at MaineHealth until all HSR training, COI disclosure, and required ancillary reviews and certifications have been satisfied.

#### **8.3.4 Institutional Registration Requirement:**

Studies that will be reviewed by external IRBs must be registered with MaineHealth, via submission of the following documents in IRBNet:

- MaineHealth SmartForm Wizard
- ICH GCP Supplemental Form
- Current Protocol
- Local Subject Materials (assessment tools, questionnaires, data collection forms, survey instruments, interview questions, screening forms, etc.)
- Local Recruitment Materials (e.g. advertisements, letters, radio or t.v. scripts, broadcast messages, etc.)
- Local Telephone Scripts/Screeners (including those for receipt of calls in response to general advertisements)
- The Proposed or previously approved Consent/Parental Permission/Assent Form(s) in Word Format
- Documentation of Departmental Review (signed form or email)
- Internal Services Sign-off (as applicable)
- Letter(s) of permission from any non-MaineHealth sites; or when applicable documentation of IRB approval or exemption from external sites, if not otherwise documented (by reliance agreements, contracts etc.)
- Patient Reimbursement Information (if applicable)
- IF USING WIRB, WIRB smartform (at time of initial submission and renewal submissions)
- If MaineHealth is to be the privacy board for the study:
  - Submission Form: HIPAA Request for Waiver or Alteration of Authorization (if applicable)
  - Submission Form: HIPAA Certification Form - Deidentification (if applicable)
  - Submission Form: HIPAA Certification Form - Limited Data Set (if applicable)

ORC will review the information and verify that CITI training, COI review, and any other applicable approvals or requirements have been completed, and determine the need for relaying local context information to the external IRB in accordance with the reliance agreement. Where waivers or alterations of HIPAA authorization are requested, and the external IRB will not be responsible for review (e.g., studies reviewed by the NCI CIRB), the ORC Staff member will forward such requests to an MaineHealth IRB Chair or a designated expedited reviewer for review. ORC will notify the investigators by e-mail or via IRBNet once the proposed research has been cleared for submission to the external IRB. Once approved by the external IRB, investigators must submit in IRBNet a copy of the approval letter and any approved consent document(s). If the protocol was modified during the external IRB review process, the approved version of the protocol should be provided as well.

### **8.3.5 Post-IRB Approval Requirements:**

- Unless the external IRB's reporting process provides for simultaneous notification to ORC, Investigators approved through external IRB review will report in IRBNet:
  1. Findings from DSMB meetings that have occurred (if drives a change to the study)
  2. Audit or inspection reports (including internal audits, if applicable)

3. Local unanticipated problems, complaints, and any noncompliance that meet local reporting criteria (serious AND unanticipated AND possibly related to the research);
4. Changes in PI or study personnel

In general, Investigators are reminded that all other Institutional reporting requirements remain applicable in addition to HRPP reporting requirements. The documentation provided to the external IRB for these events will suffice for submission to the ORC. Such submissions will be reviewed by ORC to ensure that the conduct of the study meets institutional requirements for compliance and continuation of the study.

#### **8.4 Exceptions to IRB vs. Local Site Responsibilities**

Certain areas of responsibility can be handled by either the reviewing IRB or the local site HRPP, provided they have been agreed to in the reliance agreement or outlined in a companion document. For example, alternative procedures may be used for any of the following:

1. Conducting and documenting scientific review
2. Management and documentation of ancillary reviews and institutional permissions for research;
3. Training requirements and verification of qualifications and credentials for external investigators and staff;
4. For-cause and not-for-cause compliance reviews;
5. Site-specific consent language;
6. HIPAA compliance;
7. Handling of matters concerning noncompliance, including which institution is responsible for deciding whether each allegation of non-compliance has a basis in fact, whether an incident of noncompliance constitutes serious or continuing noncompliance, and who will handle reporting to federal agencies;
8. Handling of unanticipated problems, and responsibility of reporting to federal agencies when required;
9. Review of grant and IRB protocol for congruence;
10. Review of investigator financial disclosures for COI (note: the reviewing IRB must provide final approval of any management plans generated to mitigate investigator FCOI);
11. Managing organizational conflict of interest relating to the research
12. Procedures for submission and review of interim reports and continuing review materials; and/or
13. The communication of IRB determinations and other information to external investigators and organizations.
14. In the case of the termination of a reliance agreement, identification of the party responsible for continued oversight of active studies until closure or a mutually agreed upon transfer of the study.

## 9 NIH Single IRB (sIRB) for Multi-Site Research

The NIH sIRB policy applies to grant applications proposing non-exempt human research which are received for due dates on or after January 25, 2018. For contracts, the policy applies to all solicitations issued on or after January 25, 2018. The policy does not apply to career development, research training, or fellowship awards, nor to sites that are not conducting the same protocol as the other sites (e.g., sites providing statistical support or laboratory analysis only) or to foreign sites.

Exceptions to the policy are automatic when local IRB review is required by federal, tribal, or state law/regulation/policy. Such exceptions and the basis should be cited in the proposed sIRB plan (see below) and apply only to the site(s) to which the law/regulation/policy applies. Other exceptions will be considered when there is compelling justification. The site(s) and justification for why the site(s) cannot rely on the single IRB of record should be included in the proposed sIRB plan. NIH will consider the exception request and inform the applicant of the outcome.

### 9.1 Selection and Designation of a sIRB

MaineHealth investigators submitting applications for NIH-funded multi-site research must describe the sIRB plan in the funding proposal (grant application or contract proposal), and, if applicable, may request direct cost funding to cover additional costs related to the requirements of the NIH policy.

**ORC should be contacted as early in the grant writing process as possible** to either confirm that MaineHealth can provide IRB services for the study, or to assist the investigator in making alternative arrangements (e.g., use the IRB at one of the participating sites, SMART IRB, etc.). ORC will consult with others within the organization as needed and make a recommendation to the IO for consideration. If MaineHealth IRB can serve as the sIRB, ORC will assist the investigator in working with the Grants and Contracts Office to ensure accurate, direct cost, budgeting for the service.

### 9.2 Reliance Agreements for sIRB Studies

A Reliance Agreement (or “Authorization Agreement”) between the sIRB and the participating sites is required. See Section 9.2 for details.

### 9.3 sIRB Responsibilities

1. Per the NIH Policy, the sIRB is responsible for conducting the ethical review of NIH-funded multi-site studies for participating sites and for carrying out the regulatory requirements as specified under the HHS regulations at 45 CFR Part 46.
2. The sIRB must have the necessary infrastructure to support the required activities (e.g., administrative or regulatory staff, policies, procedures, workflows and technology).
3. In reviewing multi-site research protocols, the sIRB may serve as a Privacy Board, as applicable, to fulfill the requirements of the HIPAA Privacy Rule for use or disclosure of protected health information for research purposes.
4. The sIRB can delegate to relying institutions the ability to monitor or observe the conduct of the research and/or the consent process.

5. The sIRB must review and approve proposed management plans for investigators determined to have a financial conflict of interest.

#### **9.4 Participating Site Responsibilities**

All sites participating in a multi-site study are expected to rely on a sIRB to carry out the functions that are required for institutional compliance with IRB review set forth in the HHS regulations at 45 CFR 46. Participating sites are responsible for meeting other regulatory obligations, such as obtaining informed consent, overseeing the implementation of the approved protocol, and reporting unanticipated problems and study progress to the sIRB. Participating sites must communicate relevant information necessary for the sIRB to consider local context issues and state/local regulatory requirements during its deliberations. Participating sites are expected to rely on the sIRB to satisfy the regulatory requirements relevant to the ethical review. Although IRB ethical review at a participating site would be counter to the intent and goal of this policy, the policy does not prohibit any participating site from duplicating the sIRB. However, if this approach is taken, NIH funds may not be used to pay for the cost of the duplicate review. Additionally, the participating site is responsible for:

1. Reporting incidents of protocol deviations or noncompliance to the sIRB;
2. Monitoring or observing the conduct of the research and/or the consent process, when specified in the Reliance Agreement;
3. Ensuring disclosure and management of conflicts of interest according to the participating sites' policies and procedures and submit for approval to the sIRB management plans related to investigator FCOI's in human subject research;
4. Reporting to the sIRB changes to research implemented to eliminate apparent immediate hazards to participants;
5. Ensuring ancillary reviews by Pharmacy, IBC, Radiation Safety Committee, Scientific Review Committee, etc. are conducted prior to commencement of the research (or IRB approval of the research, depending on local policy).

When an external IRB serves as the sIRB for a study in which MaineHealth is engaged, investigators must register the study with MaineHealth via IRBNet prior to submission to the external IRB following the procedures outlined in Section 8.3.4. Post-approval requirements for investigators are also detailed in Section 8.3.5. Research reviewed by external IRBs remains subject to review, approval, and oversight by MaineHealth HRPP and must adhere to all applicable policies, procedures, and requirements required for the safe and ethical conduct of the study.

## **10 MaineHealth Institutional Review Board**

MaineHealth has established one Institutional Review Board (IRB) to ensure the protection of human subjects in research conducted its auspices.

### **10.1 IRB Authority**

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

1. To approve, require modifications to secure approval, or disapprove human subjects research activities;
2. To require that informed consent is obtained and documented in accordance with regulatory and policy 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 10.6. 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, for example, the director of grants and contracting, the vice president for research, or deans of research who are responsible for raising funds or garnering support for research may serve on the IRB

Research that has been reviewed and approved by the IRB may be subject to review and disapproval by officials of MaineHealth. 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 committee, office, or person. 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 organizational reviews.

## **10.2 Roles and Responsibilities**

### **10.2.1 Chair of the IRB**

The IO, in consultation with the ORC Director and the IRB Manager appoints a Chair and Vice Chair of the IRB. Any change in appointment, including reappointment or removal, requires written notification.

The IRB Chair should be a highly-respected individual, 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 departments.

The IRB Chair is responsible for conducting IRB meetings and 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 subjects may be at risk of harm, when serious noncompliance may have occurred, 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 IO, the ORC Director, and the IRB Manager about IRB member performance.

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

### **10.2.2 Vice Chair of the IRB**

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

The performance of the IRB Vice Chair will be reviewed on an annual basis by the ORC Director in consultation with the IO, IRB Manager, and ORC Staff. Feedback from this evaluation will be provided to the Vice Chair. If the Vice Chair is not acting in accordance with the IRB's mission, following policies and procedures, has an undue number of absences, or is otherwise not fulfilling their responsibilities, s/he may be removed.

### **10.2.3 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:

- Completing member education and training, both initial and on-going (See Section 3.1)
- Maintaining the confidentiality of IRB deliberations and research reviewed by the IRB
- Conducting and documenting reviews in a timely fashion
- Attending IRB meetings as scheduled
- Recusing self from reviewing or voting on research when s/he has a conflict of interest (See Section 25.2)
- Participating in subcommittees of the IRB if requested and available
- Conducting themselves in a professional and collegial manner

Members should attend all meetings for which they are scheduled. If a member is unable to attend a scheduled meeting, they should inform the IRB Manager and/or the ORC Staff. If a member's availability changes and they are no longer able to regularly attend IRB meetings or will be absent for an extended period of time, they should inform the IRB Manager. The Manager will assess the situation, including the availability of the alternate when applicable, and make recommendations to the ORC Director and the IRB Chair to ensure that the IRB is able to meet quorum requirements and has the necessary expertise to review the research which regularly comes before it.

The performance of IRB members will be reviewed on an annual basis by the ORC Director, the IRB Manager, the ORC Staff, and the IRB Chair. Feedback from this evaluation will be provided to IRB members. Members who are not acting in accordance with the IRB's mission, not following policies and procedures, have an undue number of absences, or are otherwise not fulfilling the responsibilities of membership, may be removed by the IO or his/her designee.

#### **10.2.4 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, in part or in full, or when the regular member has a conflict of interest in regard to a protocol under review. 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 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. When both the regular member and the alternate is in attendance at an IRB meeting, only one may be counted towards quorum and vote. 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.

#### **10.2.5 Subcommittees of the IRB**

The IRB Chair, in consultation with the ORC Director and the IRB Manager, may appoint one or more other IRB members to a subcommittee of the IRB to review issues and to make recommendations to

the IRB (e.g., to supplement the IRB's review of research proposals or to review of reports of potential unanticipated problems or noncompliance). The size and composition of the subcommittee shall depend on the scope of duties delegated by the IRB Chair. Any such subcommittee cannot approve research or issue determinations that require review by the convened IRB.

### **10.3 Composition of the IRB Membership**

The IRB must promote respect for its advice and counsel in safeguarding the rights and welfare of the research that comes before it and must possess the professional competence necessary to review specific research activities. The structure and composition of the MaineHealth IRB is based upon regulatory requirements and the characteristics of the research it reviews. A member of the IRB may fill multiple membership position requirements (e.g., nonscientific and unaffiliated).

- 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. The IRB shall not consist entirely of members of one profession
- 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
- 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
- The IRB will include members who are knowledgeable about and experienced working with vulnerable populations (e.g., children, prisoners, pregnant women, or adults with impaired decision-making capacity) that are regularly included in the research under its review
- 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 includes at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas
- The IRB 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
- The IRB includes at least one member who represents the general perspective of participants

At the discretion of the IO and ORC Director, IRB staff may be appointed as IRB members or alternates.

Individuals from the MaineHealth Grants and Contracts Office, the Development Office, or the Intellectual Property Officer may not serve as members of the IRB or carry out day-to-day operations of the IRB. Individuals from these offices may provide information to the IRB and attend IRB meetings when invited as guests.

On an annual basis, the IRB Chair, the IRB Manager, and the ORC Director review the membership and composition of the IRB to determine if it continues to meet regulatory and organizational requirements.

### **10.3.1 Appointment of Members to the IRB**

When the need for a new IRB member or alternate is identified, the ORC Director, the IRB Manager, and ORC Staff work together with the IRB Chair to obtain qualified candidates. Attendings and Staff of MaineHealth and others may forward recommendations to the Institutional Official, ORC Director, or to the ORC.

The final decision in selecting a new member is made by the IO, in consultation with the ORC Director, the IRB Manager, and the IRB Chair.

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 ORC Director, IRB Manager, and/or the IO.

The ORC Director will ensure that changes in IRB membership are reported via the federal IRB registration in accordance with the instructions provided on [OHRP's website](#).

### **10.4 Liability Coverage for IRB Members**

All IRB members have liability insurance coverage as part of their IRB membership in their capacity as agents of the Maine Medical Center.

### **10.5 Use of Consultants**

When necessary, the ORC Director or IRB Manager may solicit individuals from within or outside the organization with the expertise to assist in the review of research or issues which require expertise beyond or in addition to that available on the IRB. The IRB Office will ensure that all relevant materials are provided to the consulting reviewer prior to the convened meeting or expedited review.

The ORC Director or IRB Manager reviews the COI 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 will not be invited to provide consultation.

The consultant's findings will be presented to the IRB for consideration either in person or in writing. If in attendance at an IRB meeting, consultants may provide information and assist in the IRB's deliberations, but may not participate in the vote.

Written statements from consultants will be kept in the IRB records. Information provided by consultants at IRB meetings will be documented in the minutes.

*Ad hoc* or informal consultations requested by individual members (rather than the convened board) will be managed in a manner that protects the investigator's confidentiality and that complies with the IRB COI policy.

## **10.6 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 ORC Director or IO. 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 the Chief Academic Officer for investigation and any necessary action.

Undue influence means attempting to interfere with the normal functioning and decision-making of the IRB, or to attempt to influence an IRB member or staff member or any other member of the research team, outside of the established 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.

## 11 IRB Actions, Failure to Respond, Appeals

### 11.1 IRB Actions

In conducting its review of research, the IRB may take any of the following actions. With the exception of disapproval, the actions listed below may be used for either expedited or convened board review. Disapproval can only be decided at a convened IRB meeting. An expedited reviewer cannot disapprove a study.

**Approval.** The research, proposed modification to previously approved research, or another 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.

**Approved with Conditions.** 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 will designate the final reviewer from among the IRB members to receive responsive materials from the investigator and to determine that the conditions have been satisfied. 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:

1. The date when the IRB determined that the criteria for approval were satisfied (i.e., the "approval date");

2. The date when verification was made that all IRB conditions have been satisfied (i.e., the “effective date”), and;
3. For initial approval and continuing reviews, the date by which continuing review must occur (i.e., the “expiration date”)

The IRB will be informed of the outcome of this expedited review of the investigator’s response in the agenda of the next meeting.

**Deferred.** An IRB action taken when the convened IRB cannot fully evaluate the research under review and make the determinations required for approval without modifications to the protocol and/or informed consent document, or submission of clarifications or additional materials prior to reconsideration of the research. *Note: Convened IRB review of the investigator’s response(s) is required.*

**Not Approved.** An IRB action taken when the determinations required for approval of research cannot be made, even with substantive clarifications or modifications to the protocol and/or informed consent process/document. *Note: Research cannot be disapproved by expedited review.*

**Tabled without Action.** An IRB "action" that indicates that review was not initiated or was not completed, resulting in postponement of IRB review, usually due to loss of quorum or other administrative issue. Research tabled at a convened meeting will be reviewed at a future convened meeting.

## **11.2 Failure to Respond**

Upon review of a research study, the IRB may require changes or request certain information from an investigator. Failure to respond to IRB required changes or requests for information within sixty (60) days (or less if the IRB determines that the information must be submitted earlier to ensure protection of the research subjects) may result in suspension or termination of IRB approval for the study. For studies that have not yet been approved, the study submission may be administratively withdrawn. At its discretion, the IRB may grant an extension beyond sixty (60) days if the investigator contacts the IRB office prior to the deadline and presents sufficient cause for delay.

## **11.3 Reporting IRB Actions**

All IRB actions are communicated to the investigator, and/or the designated contact person for the research study, via the publication of a letter in IRBNet within ten (10) working days, whenever possible, of the review. When applicable, a stamped copy of the approved consent form, parental permission form, and/or assent form will also be published. For IRB actions of approved with conditions, disapproval, or tabled, the notification will include a listing of the conditions or requirements that must be satisfied or responded to.

The IRB reports its findings and actions to the organization in the form of its minutes, which are accessible to, and regularly reviewed by, the MaineHealth IO.

#### **11.4 Appeal of IRB Decisions**

When the IRB suspends, terminates, or disapproves research, the IRB letter communicating the decision will include the basis for the action and will offer the investigator the opportunity to respond in person or in writing. Additionally, whenever an investigator disagrees with an IRB requirement or decision, or believes that providing the IRB with additional information may result in a different outcome, they may request that the IRB reconsider its decision by submitting a memo and other supportive materials via IRBNet. The investigator may be invited to attend the IRB meeting to discuss the request and provide information, but will be asked to leave prior to the IRB's final deliberations and vote.

## 12 IRB Review Process

The MaineHealth IRB will review and ensure that research under its oversight 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

### 12.1 Expedited Review

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

- 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
- Minor changes in research previously approved by the convened IRB. 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.

#### 12.1.1 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 (i.e., the change does not increase the level of risk);
2. The research design or methods (adding procedures that are not eligible for expedited review (See Section 12.1.2) would be considered more than a minor change);
3. The number of local subjects to be enrolled in the research (usually not greater than 10% of the total requested);
4. The qualifications of the research team (i.e., the change does not negatively impact the expertise available to conduct the research);
5. The facilities available to support safe conduct of the research; or
6. Any other factor which would warrant review of the proposed changes by the convened IRB.

Minor changes also include the addition of sites to a protocol approved by the convened IRB as long as the investigator(s)/site(s) do not have a conflict of interest, potential compliance concerns (e.g., a 483 that has not been adequately resolved), or any other investigator or site-specific concerns (e.g., qualifications, facilities, or resources to safely conduct the research).

### **12.1.2 Categories of Research Eligible for Expedited Review**

MaineHealth 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.

#### **Expedited Categories one (1) through seven (7) may be used for both initial and continuing review:**

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
  - a. Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)
  - b. Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
  - a. From healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8-week period and collection may not occur more frequently than 2 times per week; or
  - b. From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period and collection may not occur more frequently than 2 times per week. (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 nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization; (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 nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the DHHS regulations for the protection of human subjects. See Exempt Categories and 45 CFR 46 101(b)(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 MaineHealth 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 MaineHealth 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 MaineHealth 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:
  - a. The research is not conducted under an investigational new drug application (IND) or an investigational device exemption (IDE); **and**
  - b. Expedited review categories (2) through (8) do not apply to the research; **and**
  - c. 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**
  - d. 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.)

### 12.1.3 MaineHealth (Flex Policy) Expedited Categories

This policy creates expedited categories not found in the federal regulations, for projects that are not federally funded, are not covered by other laws or regulations that would prohibit such flexibility, and do not directly conform to expedited categories 1-9 according to 45 CFR 46. These projects will be reviewed using an approval process identical to that used for expedited research categories 1-9 under 45 CFR 46. MaineHealth Expedited Category 2c: *Collection of blood samples by finger stick, heel*

*stick, ear stick, or venipuncture.* From 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 collection from healthy, nonpregnant adults who weigh at least 110 pounds, the amounts drawn may not exceed 550 ml in an 8 week period. For collection from other adults and children, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period.

#### **12.1.4 Expedited Review Procedures**

Under an expedited review procedure, IRB review of new studies is carried out by an experienced reviewer (i.e., having served on an IRB for at least one year), or by the Expedited Review Subcommittee (ERS). Members are volunteers from the MaineHealth IRB, or may be appointed by the ORC Director, with consultation by the IRB Manager, IRB Chair, and Vice Chair. As MaineHealth considers the ERS to be a valuable training experience for newer members, this workgroup is inclusive and open to any IRB member who wishes to volunteer. Membership is monitored to ensure that experienced members serve and mentor the newer members.

The ERS meets weekly as necessary, with no quorum requirement other than the presence of at least one experienced reviewer, as defined above. Each agenda item is shared with all ERS members (generally three (3) business days before the meeting). All members of the ERS are expected to review the submission in detail for discussion at the meeting. ERS members do not participate in the review of research in which they have with a conflict of interest (see Section 25.2) but may answer questions about the research if requested.

When reviewing new research proposals under an expedited review procedure, the reviewer(s), will receive and review the same materials that would be reviewed if the research were to be reviewed by the convened IRB. For expedited review of previously approved research, the reviewer(s) will have access to the study history. The reviewer evaluates and documents whether the research qualifies for expedited review using the reviewer checklist. If the research does not meet the criteria for expedited review, the reviewer will indicate that the research requires review by the convened IRB. The submission will then be placed on the next available IRB meeting agenda.

In reviewing the research, expedited reviewers will apply the same criteria for review and approval of research described throughout this manual and may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may only be disapproved by the convened IRB.

Reviewers will use the appropriate reviewer checklist (e.g., initial, modification, continuing) to assess the criteria for approval and to document their review. For initial and continuing reviews, the documentation will include the category(ies) under which the research qualifies for expedited review. The checklists will be uploaded and maintained in IRBNet, along with an ORC summary of controverted issues discussed by the ERS, and their resolution. When expedited review is carried out and members of the ERS disagree, the IRB Chair may be consulted to make a final determination or refer the submission to the convened IRB for review.

Modifications required to secure approval will be communicated to the investigator by the ORC staff. Final approval letters will be published in IRBNet by the ORC staff.

### **12.1.5 Informing the IRB**

Members of the IRB will be apprised of expedited review approvals by means of a list provided in the agenda for the next scheduled meeting. Any IRB member can make a request to review the materials for any study by contacting the ORC Staff to gain access in IRBNet.

## **12.2 Convened IRB Meetings**

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

### **12.2.1 IRB Meeting Schedule**

The IRB meets on a regular basis throughout the year (usually once per month). The schedule for the IRB may vary due to holidays, lack of quorum, or other reasons. The schedule for IRB meetings is posted on the ORC website ([www.mmcri.org](http://www.mmcri.org)). Special meetings may be called as needed by the Chair, IRB Manager, or ORC Director.

### **12.2.2 Preliminary Review**

The [IRB Manager/ORC staff] will perform a preliminary review of all submissions for determination of completeness and accuracy, including all elements of informed consent checklist, when applicable. Only complete submissions will be placed on the IRB agenda for review. The investigator will be informed via IRBNet or e-mail of missing materials and any recommended changes. If an investigator is submitting for the first time or is not well-versed in submission procedures, consultations can be arranged with ORC Staff.

### **12.2.3 Primary and Secondary Reviewers**

After it has been determined that a submission is complete, ORC Staff, in consultation with the IRB Chairs, 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. A "primary reviewer" will be assigned to each submission and will receive and review the full submission materials. 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 10.5). 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:

- Performing an in-depth review of the submission materials and having a thorough understanding of the details
- Leading the discussion at the IRB meeting, by providing a summary and leading the IRB through the regulatory criteria for approval and any required determinations

- Completing all applicable IRB reviewer checklists

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 process and form(s)).

**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 if possible, providing that they have the necessary expertise and sufficient time to review the materials in advance of the meeting. Absent reviewers can submit their written comments for presentation and consideration 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.

#### **12.2.4 Materials received by the IRB**

All required materials need to be submitted to the ORC via IRBNet by the published deadline for inclusion on the IRB meeting agenda. On occasion, when a review is time-sensitive, the ORC may make an exception to this rule provided that there is still sufficient time for all members to review the submission materials. The meeting agenda will be prepared by ORC staff in consultation as needed with the IRB Chair or IRB Manager as needed. All IRB members receive the IRB agenda, prior meeting minutes, applicable business items, and research submission materials at least five (5) business days before the scheduled meeting to allow sufficient time for review. On occasion, a time-sensitive item may be added to the agenda less than five (5) business days in advance if circumstances warrant and the IRB staff have contacted the IRB members and verified that they will have sufficient time for review.

All IRB members have access in IRBNet to all materials submitted for all studies on the agenda, which include the following:

- MaineHealth Smartform Wizard-The application or submission form (e.g., ‘Research Application’, ‘Progress report, Study completion, and RNI Form’, modification request [via ‘Research Application’], etc.)
- Supplemental Forms as required (e.g., for inclusion of children, pregnant women, use of drugs or devices, research that plans on storing data/specimens for future use, collaborative research, translational research)
- Protocol
- The proposed Consent/Parental Permission/Assent Form(s) in Word format
- Documentation of Departmental Review (signed form or email)
- Proposed recruitment materials (e.g. advertisements, letters, radio or t.v. scripts, broadcast messages, etc.) intended to be seen or heard by potential study participants

- Telephone Scripts/Screeners (including those for receipt of calls in response to general advertisements)
- The grant application(s), if the project is federally-funded and MaineHealth is the IRB or serving as the IRB of record for the prime awardee
- Results of internal Scientific Review and Reviewer Sheets
- The Investigator Brochure(s) or package insert
- Data Sharing Plan (for NIH-funded research that generates large-scale human genomic data, including GWAS studies)
- Subject Materials (assessment tools, questionnaires, data collection forms, survey instruments, interview questions, screening forms, etc.)
- Supplement\_E\_Waiver\_Alteration\_Consent
- Request for Waiver-Alteration of HIPAA Authorization
- HIPAA Certification- Limited Data Set (LDS)\* [Fully executed Data Use Agreement to be submitted AFTER IRB approval, for studies where PHI is leaving Maine Health (the covered entity).]
- Internal Services Sign-off
- IND/IDE Documentation from FDA (if evidence is not provided in other documentation)
- Letter(s) of permission from any non-MaineHealth sites; or when applicable documentation of IRB approval or exemption from external sites
- Data Safety Monitoring Plan Information (if not described in the protocol)
- Data Safety Monitoring Board/Committee Charter (if not described in the protocol)
- Patient Reimbursement Information
- When Tufts students are the subjects in a research study, a Letter of Support from the Dean

Additionally, for HHS-supported multicenter clinical trials, the IRB should receive and review a copy of the HHS-approved sample consent form(s) and the complete HHS-approved protocol, if they exist.

If an IRB member requires additional information to complete the review, they may contact ORC or the investigator. Any additional information should be provided to the other members.

Primary reviewers will complete any applicable reviewer checklists, which serve as a guide for the review and a tool for summarizing recommendations prior to board discussion.

### **12.2.5 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.

ORC staff will confirm that quorum is present before advising the IRB Chair that it is acceptable to call the meeting to order. The IRB Chair, with the assistance of the ORC 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, or losing all non-scientific members or another required member, the IRB may not take votes until quorum is restored. When IRB members leave the meeting room, ORC Staff will document the time of departure and notify the IRB Chair if a quorum is not present.

It is generally expected that at least one individual whose primary interest is scientific, at least one individual whose primary interest is non-scientific, at least one non-affiliated individual, and at least one member who represents the general perspective of participants (one individual can serve in more than one capacity) will be present at all IRB meetings. The IRB may, on occasion, meet without this representation; however, this should be the exception (i.e., no more than 25% of meetings).

When the IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or adults with impaired decision-making capacity, one or more individuals (e.g., IRB members, alternate members, or consultants) who are knowledgeable about and experienced with such 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. When 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 may be considered by the attending IRB members but may not be counted as votes or to satisfy quorum requirements for convened meetings.

#### **12.2.6 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. Minor revisions/corrections may be verified by the IRB Chair or Vice Chair outside of the meeting.

The IRB reviews submissions for initial and continuing review, requests for modifications to previously approved research, and other business items, as applicable (e.g., potentially serious noncompliance). The Primary and Secondary Reviewers present an overview of the submission and assist the Chair in leading the IRB through the evaluation of the regulatory criteria for approval or other required determinations using their checklist(s) as a guide. ORC staff project on the presentation screen materials relevant to the board's review and discussion to facilitate the review process. For the

research to be approved, or any motion on a business item of the agenda to pass, it must receive the approval of a majority of those voting members present at the meeting.

ORC staff are responsible for taking minutes at each IRB meeting.

### **12.2.7 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 ORC Director, the IRB Manager, and the ORC staff regularly attend IRB meetings and may participate in the IRB discussion and deliberations, but may not vote unless attending as a member or alternate.

Other guests may be permitted to attend IRB meetings at the discretion of the IRB Chair and/or the IRB Manager. All guests are asked to sign a confidentiality agreement and will not participate in discussion unless requested by the IRB; under no circumstances may they vote.

### **12.3 Criteria for IRB Approval of Research**

For the IRB to approve human subjects research, either through expedited review or by the convened IRB, it must determine that the following requirements are, or remain, satisfied.

1. Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
3. Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by the Federal Regulations [[45 CFR 46.116/21 CFR 50](#)].
5. Informed consent will be appropriately documented, in accordance with, and to the extent required by the Federal Regulations [[45 CFR 46.117/21 CFR 50](#)].

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.

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.

### **12.3.1 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 or undergo even if not participating in the 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 that can reasonably be expected to result from the research.

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.

The IRB should not consider any compensation that subjects may receive to be a benefit of the research.

When research subjects are assigned to different arms or otherwise undergo differing interventions, procedures, or exposures, the evaluation of risk and benefit should be made for each subject group (i.e., a “component analysis”). This is especially important when a subset of subjects will have no possibility of direct benefit but will be exposed to greater than minimal risks.

#### **12.3.1.1 Scientific or Scholarly Review**

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

- The research uses procedures consistent with sound research design; and
- The research design is sound enough to yield the expected knowledge.

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 a duly constituted local or external scientific review committee. Any study that is investigator-initiated and determined to be greater than minimal risk must undergo scientific review prior to undergoing ethical and regulatory review by the MaineHealth IRB. MMCRI shall maintain a scientific review committee for this purpose, as needed.

When scientific or scholarly review is conducted by an individual or entity external to the IRB, documentation of the outcome, and details of that review must be provided to the IRB for review and consideration. The MaineHealth IRB application asks whether scientific or scholarly review has been performed, and, if yes, requests that a copy of that review be provided with the submission. A determination by the IRB regarding the adequacy of the scientific review will be an integral part of the IRB assessment.

#### **12.3.2 Equitable Selection of Subjects**

The MaineHealth IRB evaluates whether the selection of subjects is equitable with respect to gender, age, class, etc. by reviewing the IRB application, protocol, and other materials and information. The MaineHealth 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 evaluates whether subject selection has been equitable.

### **12.3.2.1 Recruitment of Subjects**

The investigator will provide the IRB with a plan for recruitment of 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 12.4.9 for a discussion of IRB review of advertisements and Section 12.4.10 for a discussion of IRB review of payments.

### **12.3.3 Informed Consent**

The IRB will ensure that informed consent will be sought from each prospective subject or the subject's legally authorized representative (LAR), 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 15 for a detailed discussion on informed consent.

### **12.3.4 Data and Safety Monitoring**

For research that is more than minimal risk, the investigator should submit a data and safety monitoring (DSM) 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 providing DSM findings to the IRB. DSM may be performed by a researcher, medical monitor, safety monitoring committee, or other means.

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

The principles the IRB applies in evaluating the adequacy of a proposed DSM plan include:

- Monitoring should be commensurate with the nature, complexity, size, and risks of the research
- Monitoring should be timely. Frequency should be commensurate with risk. Conclusions are reported to the IRB
- For low risk studies, continuous, close monitoring by the study investigator or an independent party may be an adequate and appropriate format for monitoring, with prompt reporting of problems to the IRB, sponsor, and regulatory bodies, as applicable
- For greater than minimal risk studies that do not include a plan for monitoring by a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), and that are blinded, multi-site, involve vulnerable populations, or involve high-risk interventions or procedures, the IRB

will carefully evaluate the proposed DSM plan and may require establishment of a DSMB, DMC, or other methods to enhance the monitoring and management of safety

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

For a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), the plan should also include a charter (either as a part of the protocol, or as an appendix) that describes the composition of the board or committee. Generally, a DSMB or DMC 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.

The National Institutes of Health (NIH) requires the establishment of DSMBs for multi-site clinical trials involving interventions that entail potential risk to the participants.

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.

### **12.3.5 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**.

#### **12.3.5.1 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 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).

**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.

#### **12.3.5.2 Privacy**

The IRB must determine whether the activities in the research appropriately protect the privacy of potential and enrolled 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 privacy, consideration is given to the:

- Methods used to identify and contact potential participants
- Settings where recruitment and research activities will occur
- Appropriateness of personnel and others present for research activities
- Methods to verify the identity of subjects prior to disclosing information (e.g., with phone calls)
- Methods used to obtain information about participants, and the nature of the requested information, including whether the data is the minimum necessary to achieve the aims of the research
- 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"

#### **12.3.5.3 Confidentiality**

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

The IRB assesses whether there are adequate provisions to protect data confidentiality by evaluating 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. 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 regarding the use, maintenance, storage, and transmission of information. The IRB will review the information received from the investigator and determine whether the confidentiality of research data is sufficiently protected. In some cases, the IRB may also require that a Certificate of Confidentiality is obtained to protect data from compelled disclosure (See Section 28.2).

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. The IRB will 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 will 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](#).

### **12.3.6 Vulnerable Populations**

Certain individuals, by nature of their age or mental, physical, economic, educational, employment, or other circumstances, may be more vulnerable to coercion or undue influence than others. At the time of initial review, and when a proposed modification includes the involvement of vulnerable subject populations, the IRB will consider the scientific and ethical reasons for including vulnerable subjects in research. When appropriate, the IRB may determine and require that 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 process for specific populations of vulnerable subjects, please refer to Section 16.

## **12.4 Additional Considerations**

### **12.4.1 Determination of Risk Level**

At the time of initial review, the IRB will make a determination regarding the risks associated with the research. Risks associated with the research will generally be classified as either "minimal" or "greater than minimal" with additional classifications as required by the various subparts or FDA regulations. Risk determinations may vary over the life of a research study depending on the procedures and risks that subjects will be exposed to as the research progresses. Because of this, the IRB may reevaluate the risk determination with modifications to the research, at continuing review, and when new

information becomes available. 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.

#### **12.4.2 Period of Approval**

At the time of initial review and at continuing review, the IRB will make a determination regarding the period of approval. 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, 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.

IRB approval is considered to have lapsed at the end of the day of the expiration date of the approval (i.e., the expiration date is the last day research can be conducted). 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) when it has been 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 is no later than one year from the effective date of initial IRB approval (for expedited reviews), and no later than one year from the last full committee review (for full reviews).

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. As a courtesy, the IRB electronic system sends reminders to the investigator prior to the study's expiration date, notifying him or her that the study is due for a continuing review or when approval has expired.

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 before 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.

#### **12.4.3 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 noncompliance on the part of the investigator; and
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 enrolled subjects. If a maximum number of subjects is used to define the approval period, it is understood that the approval period in no case can exceed one year and that the number of subjects enrolled determines the approval period only when that number of subjects is enrolled in less than one year. If an approval period of less than one year is specified by the IRB, the reason for more frequent review must be documented in the minutes or the expedited reviewer's checklist.

#### **12.4.4 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 occurred during the IRB-designated approval period.

In support of this requirement, the MaineHealth IRB requires the submission of Other Reportable Information (See Section 21) including reports from external monitors, auditors, or inspectors (See Section 2.1).

The IRB will also 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:

##### **For non-FDA regulated research:**

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. Whether concerns 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 organization or the IRB;

6. Research without any routine independent monitoring;
7. Any other factors the IRB deems verification from outside sources is relevant.

**For FDA regulated research:**

1. The nature of and any risks posed by the clinical investigation.
2. The degree of uncertainty regarding the risks involved.
3. The vulnerability of the participants.
4. The experience of the clinical investigator in conducting clinical research.
5. The IRB's or EC's previous experience with that researcher or sponsor (e.g., compliance history, previous problems with the researcher obtaining informed consent, prior complaints from participants about the researcher).
6. The projected rate of enrollment.
7. Whether the study involve novel therapies.

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 19 on Noncompliance).

**12.4.5 Consent Monitoring**

In reviewing the adequacy of informed consent procedures for proposed research, the IRB may on occasion determine that 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 where recruitment will occur in situations or circumstances that may negatively impact the consent process (e.g., the Emergency Room);
4. Studies involving highly vulnerable populations (e.g., ICU patients, children who are wards);
5. Studies involving study staff with minimal experience in administering consent to potential study participants; or
6. Other situations when the IRB has concerns that consent process may not be/is not being conducted appropriately (e.g., prior investigator noncompliance, 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 may consult with the ORC Director, SEQuR staff, and others to develop an appropriate plan. The consent monitoring may be conducted by the ORC staff, IRB members, or another appropriate designee. The investigator will be notified of the IRB's determination and the reasons for the determination. Arrangements will be made with the investigator for monitoring of the consent process, typically for a specified number of subjects. When warranted, the investigator may not be notified until after the observation has occurred. When observing the consent process, the monitor will evaluate whether:

1. The informed consent process was appropriately conducted and documented;
2. The participant had sufficient time to consider study participation, and to ask questions and have them answered;
3. The consent process involved no coercion or undue influence;
4. The information was accurate and conveyed in understandable language; and
5. The subject appeared to understand the information and provided their voluntary consent.

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

#### **12.4.6 Investigator Qualifications**

The IRB reviews credentials, curriculum vitae, resumes, training, or other relevant materials to determine whether investigators and members of the research team are appropriately qualified to conduct the research. The IRB may rely upon other MaineHealth processes (e.g., credentialing) to inform this determination.

#### **12.4.7 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 and evaluate the impact on the subjects' rights and welfare. When 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 that the investigator contact 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. The IRB may require that the currently enrolled subjects be re-consented or otherwise provided with the new information. When appropriate, the IRB may also require that former subjects be provided with the new information (e.g., late emerging safety information).

#### **12.4.8 Conflicts of Interest (COI)**

The IRB research application solicits information about investigator and research staff COI disclosure. If a change in COI status is reported that is indicative of a new FCOI, the ORC staff will work with the Research Conflict of Interest Committee (RCOIC) to develop a management plan, if applicable. The IRB will receive the plan for review. As part of its review process, the IRB will make a final determination

regarding approval of the management plan, i.e., that it adequately addresses the COI, and protects the human subjects in the research. When there is an institutional COI, the IRB will review the conflict and the management plan provided by the RCOIC, and render a decision regarding allowance of the study to be approved. (See Section 25 for a more detailed discussion of COI).

#### **12.4.9 Advertisements and Recruitment Materials**

The IRB must review and approve all advertisements and recruitment materials prior to posting, use, or distribution. The IRB will review:

- The information contained in the advertisement/recruitment material
- The mode/method of its communication;
- The final copy of printed advertisement/recruitment material
- The proposed script and final version of any audio/video advertisements/recruitment materials

This information must be submitted to the IRB with the initial application, or, if 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 on the subject to participate. This includes, but is not limited to the following (as applicable):

1. Statements implying a certainty of favorable outcome or other benefits beyond what was outlined in the consent form and the research plan;
2. Claims, either explicit or implicit, that the test article (drug, biologic or device) or intervention is safe or effective for the purposes under investigation;
3. Claims, either explicit or implicit, that the test article or intervention is known to be equivalent or superior to any other drug, biologic, device, or intervention;
4. Using terms like “new treatment,” “new medication,” or “new drug” without explaining that the test article or intervention is investigational;
5. Promising “free medical treatment” when the intent is 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; and
8. The inclusion of exculpatory language.

Recruitment materials should be limited to the information 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 the activity is research and not treatment;
7. A brief list of potential benefits (e.g., no-cost health exam).

Once approved by the IRB, advertisements and recruitment materials cannot be altered or manipulated in any way without prior IRB approval.

Directory listings of research such as [ClinicalTrials.gov](https://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, summary description of the research, 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 review the script and procedures to ensure that the screening procedures adequately protect the rights and welfare of the prospective subjects.

#### **12.4.10 Payments and Reimbursement**

Payments to research subjects are commonly proposed as an incentive for participation in recognition of the time, effort, inconveniences, and discomforts that participation in the proposed research may entail. In contrast to payments, reimbursement is provided to cover actual costs incurred by subjects as a result of participation (e.g., travel, parking, lodging, etc.). Payment arrangements should be managed separately from reimbursement whenever possible because the ethical considerations differ (as well as the potential tax implications). Reimbursement offsets costs and may decrease financial risks associated with participation and in doing so may facilitate equitable selection of subjects. In contrast, the amount, timing, and nature of payments may unduly influence potential subjects' decision-making, influencing them to accept discomforts or risks that they otherwise would find unacceptable and interfering with truly voluntary informed consent. Payment arrangements may also create issues with equitable selection of subjects, including the societal distribution of research risks and benefits and the generalizability of the research results.

The IRB must consider the proposed amount of payment, the method and timing of disbursement, the subject population, the recruitment methods and materials, and the information provided within the proposed consent form in order to evaluate the acceptability of a proposed payment plan. The IRB does not consider payment as a benefit when weighing the risks and benefits of the research, payment is an incentive not a benefit of the research.

Investigators who wish to pay research subjects must include in their application to the IRB the amount and schedule of all payments and the justification or basis for payment. Such justification should substantiate that proposed payments are reasonable and commensurate with the time and inconveniences associated with study participation and do not constitute (or appear to constitute) undue pressure on the potential subject to volunteer for the research study.

When research involves multiple visits or interactions, payment should be prorated and not be contingent upon the participant completing the entire study. Further, any amount paid as a 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.

Plans to reimburse subjects for incurred expenses must also be outlined in the application to the IRB and described within the consent.

MaineHealth Accounts Payable follows Internal Revenue Services (IRS) guidelines for reporting purposes. Payments for all MaineHealth entities are reported in aggregate. When applicable, the consent form must disclose the information that will be collected (e.g., Social Security Number), who will be provided or have access to the information, and the circumstances that necessitate IRS reporting.

#### **12.4.11 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 course credit, totes, books, toys, or other non-monetary gifts or incentives, the approximate retail value must be described to the IRB along 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 not to participate will have not adverse effect on 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 subject's decision to participate, that they have not served to unduly influence participation.

#### **12.4.12 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 ORC and the IRB rely on MaineHealth Counsel for the interpretation and application of Maine 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.

## **12.5 Continuing Review**

The IRB will conduct continuing review of ongoing research at intervals that are appropriate to the level of risk of the research, but not less than once per year. The date by which continuing review must occur will be recorded in IRBNet and on initial and continuing review approval letters. Continuing review must occur as long as the research remains active, including when the remaining research activities are limited to the analysis of private identifiable information.

### **12.5.1 Continuing Review Process**

As a courtesy to investigators, IRBNet will send out automatic reminder notices to investigators at pre-specified intervals 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, as applicable to the research:

1. The MaineHealth Smartform Wizard-The application or submission form (e.g., 'Research Application', 'Progress report, Study completion, and RNI Form', amendment request [via 'Research Application'] etc.);
2. Supplemental Forms as required (for the inclusion of children, pregnant women, use of drugs or devices, research that plans on storing data/specimens for future use, collaborative research, translational research, Progress Report);
3. The protocol;
4. The previously approved consent/parental permission/assent form(s) in Word format;
5. A Signed, De-identified Copy of the Informed Consent Document/Parental Permission/Assent Form(s) (If a subject has been enrolled in the current approval period at renewal)
6. Reports as applicable from:
  - a. DSMB meetings that have occurred
  - b. Annual Report to FDA
  - c. Audit or Inspection Reports (including internal audits)

IRB members conducting full or expedited reviews can be granted access in IRBNet to additional study packages or be provided with any additional materials by request to the IRB staff.

### **12.5.2 IRB Considerations for Continuing Review**

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;
3. Local investigator and organizational issues; and
4. Research progress.

### **12.5.3 Convened Board Review**

In conducting continuing review of research not eligible for expedited review, IRB members are provided all of the materials listed in Section 12.5.1 and are responsible for reviewing, at a minimum, the Continuing Review Application, the current IRB-approved consent form(s) (when applicable), and any proposed modifications to the research or consent form(s). The complete IRB file and relevant IRB meeting minutes are available to IRB members in IRBNet. The Primary Reviewer is responsible for reviewing the complete materials submitted for continuing review and completing a reviewer checklist to facilitate the review and discussion at the meeting. At the meeting, the Primary and Secondary Reviewers assist the Chair by providing a summary of the research, their evaluation of the research and continuing review materials, and recommendations.

### **12.5.4 Expedited Review**

In conducting continuing review under expedited procedures, the Expedited Reviewer receives all of the previously noted materials. The continuing review checklist will be completed 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.

Generally, if research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, except in limited circumstances described by expedited review categories (8) and (9) (see Expedited Review Categories in Section 12.1.2). It is also possible that research activities that previously qualified for expedited review have changed or will change, such that expedited continuing review would no longer be permitted.

### **12.5.5 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 actions described in Section 11.

If an IRB member conducting expedited review believes that continuation of the research 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 13 for a detailed discussion of suspensions and terminations).

## 12.5.6 Lapses in Continuing Review

The regulations permit no grace period or approval extension after expiration of approval. 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 submitted the continuing review materials 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.**

When the IRB approves research with conditions at the time of continuing review before the expiration date of the preceding IRB approval period, IRB approval does not lapse if the investigator needs additional time – beyond the date on which the preceding IRB approval would have expired – to satisfy some or all of the IRB’s conditions. However, the investigator and the IRB should make every effort to resolve any conditions and finalize approval in as timely a manner as possible.

In the event that study approval does expire, IRBNet sends a notification to the investigator noting the expiration of approval and instructions that all research activities must stop. If the investigator fails to respond to the notification, and does not submit continuing review materials or a closure report within thirty (30) days, the IRB staff will refer the matter to the IRB Chair to evaluate as possible noncompliance (See Section 19).

The lapse of IRB approval due to a failure to complete continuing review and obtain re-approval prior to expiration of the previous 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 noncompliance 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. When research is subject to federal reporting mandates, the IRB must report to FDA/OHRP any instance of serious or continuing noncompliance with FDA regulations or IRB requirements or determinations.

### 12.5.6.1 Management of Enrolled Subjects During Lapse

While enrollment of new subjects cannot occur after the expiration of IRB approval, the IRB recognizes that 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 must, at the earliest opportunity, contact the IRB office and submit a request in writing via IRBNet 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, 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.

## **12.6 Modification of an Approved Protocol**

Investigators may wish to modify or amend approved research. **Investigators must seek IRB approval before making any changes, no matter how minor, into the approved research** unless the change is necessary to eliminate an apparent immediate hazard to the subject (in which case the IRB must then be notified at once).

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.

### **12.6.1 Procedures**

Investigators proposing to modify a study must submit a MaineHealth Research Application/Amendment Wizard and all supporting documents identified in the form via IRBNet for review. The modifications may not be implemented until the IRB has reviewed and approved the proposed changes. When the modification involves the addition of investigators or study personnel, the investigators/personnel may not assume any study responsibilities involving human subjects or their identifiable data until the IRB has approved their participation.

ORC staff will review the submission and make an initial determination whether the proposed changes may be approved through an expedited review process (i.e., changes to expedited research that do not alter the eligibility of the research for expedited review or minor changes to convened board studies) or whether the modification warrants convened board review. The IRB reviewer(s) using the expedited procedure has (have) 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.

### **12.6.2 Convened Board Review of Modifications**

When a proposed change in a convened board research study is not minor, or when a proposed change to an expedited study renders it no longer eligible for expedited review, the IRB must review and approve the proposed change at a convened meeting before the change can be implemented. The only exception is implementation of a change necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the IRB must be promptly informed of the change following its implementation and will review the change to determine whether it was consistent with ensuring the subjects' continued welfare.

All IRB members are provided with, and review all documents provided by the investigator. The complete IRB file and relevant IRB meeting minutes are available to IRB members upon request. The Primary Reviewer completes a reviewer checklist to facilitate the review process and discussion at the meeting.

At the meeting, the Primary Reviewer presents an overview of the proposed modifications, assists the IRB Chair in leading the IRB through the criteria for approval, and evaluates whether the modification alters any previous determinations (e.g., the risk determination), or necessitates any additional determinations (e.g., for vulnerable populations).

When the IRB reviews modifications to previously approved research, the IRB considers whether information about those modifications might relate to subjects' welfare or willingness to continue to take part in the research, and, if so, whether to provide that information to future, current, or past subjects.

### **12.6.3 Expedited review of Modifications**

An IRB may use expedited review procedures to review changes to expedited research (as long as the proposed changes would not make the research no longer eligible for expedited review) and for minor changes to studies normally subject to convened IRB review. An expedited review may be carried out by the IRB Chair or the experienced members that have been designated by the Chair or by other experienced members.

Expedited reviewer(s) complete the reviewer checklist to determine whether the modifications meet the criteria allowing review using the expedited procedure, and, if so, whether the research with the proposed modifications continues to meet the regulatory criteria for approval. The reviewer(s) will also evaluate whether the modification alters any previous determinations (e.g., a Subpart determination), or necessitates any additional determinations (e.g., for vulnerable populations).

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

### **12.6.4 Possible IRB Actions after Modification Review**

As with initial review, the convened IRB or IRB Member(s) conducting an expedited review may take any of the actions described in Section 11:

If an IRB member conducting an expedited review believes that the proposed modification(s) should be disapproved, they will refer the proposed modification(s) 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 13 for a detailed discussion of suspensions and terminations).

#### **12.6.5 Protocol Exceptions**

**Protocol 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 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 may be possible. For an exception to be approved under expedited review, the research as a whole must be eligible for expedited review, or, for convened board research, the proposed exceptions must not increase risk or decrease benefit, negatively impact the risk/benefit analysis, negatively affect the participant's rights, safety, or welfare, or negatively affect the integrity of the resultant data.

**Procedures for exceptions are the same as for a Protocol Modification.** The investigator must submit a MaineHealth Research Application/Amendment Wizard along with any new or revised materials, 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 apparent immediate hazard to the subject(s). In such cases, the exception must be submitted to the IRB as soon as possible.

#### **12.7 Closure of Research Studies**

The completion or early termination of the study, is a change in research 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 providing 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).

For multi-center research, the study may be closed once all research activities (as above) are complete at MaineHealth and any sites for which the IRB is serving as the "IRB of record". If the investigator is serving as the lead investigator or the site is the coordinating center, the study must remain open as long as the lead investigator or 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 may submit study closures to the IRB in IRBNet on Progress Report/Final Report/RNI Wizard application. 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 applying for IRB approval or exemption. 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 administrative review, and either acknowledge the closure of the study or request additional information or confirmation of facts from the investigator.

## 13 Suspensions and Terminations

### 13.1 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 18 for a discussion of unanticipated problems and Section 19 for a discussion of noncompliance.)

The IO and the ORC Director, in consultation with the IRB Chairs, have the authority to suspend or terminate the organization's approval for research. Such actions will be promptly reported to the IRB so that the IRB can review the circumstances and take any necessary actions relevant to IRB review and oversight.

**Suspension** of IRB approval is a directive of the convened IRB or IRB Chair or Vice Chair to temporarily stop some or all previously approved research activities. The IRB Chair or Vice Chair may temporarily suspend IRB approval, in part or in full, when the available information suggests that actions must be taken to protect human subjects or the integrity of the research, prior to the next convened meeting of the IRB. Temporary suspensions by the Chair or Vice Chair will be reported to the convened IRB at the next scheduled meeting at which time the convened IRB will determine if the suspension should continue, be lifted, or be modified. Suspended research studies remain open and require continuing review. Investigators must continue to provide reports 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 whether subjects should be notified and any actions necessary to ensure that the rights, safety, and welfare of subjects are appropriately protected.

The IRB will notify the investigator of suspensions in writing; a call or email may precede the written notice when appropriate. Written notices of suspensions will include a statement of the reason(s) for the IRB's action and any requirements or conditions associated with the suspension (e.g., notification of subjects). The investigator will be provided with an opportunity to respond in person or in writing.

Suspensions of IRB approval must be reported promptly to the IO, sponsors including federal department or agency heads, and federal oversight agencies as applicable. See Section 22 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 will notify the investigator of terminations in writing; a call or email may precede the written notice when appropriate. Written notices of terminations will include a statement of the reasons for the IRB's action 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, sponsors including federal department or agency heads, and federal oversight agencies as applicable. See Section 22 for a detailed discussion of reporting requirements.

### **13.2 Protection of Currently Enrolled Participants**

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

- Transferring subjects 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 subjects for safety reasons
- Requiring adverse events or outcomes to be reported to the IRB and the sponsor
- Notification of current subjects
- Notification of former subjects



## **14 Documentation and Records**

MaineHealth 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.

### **14.1 IRB Records**

IRB records include, but are not limited to:

1. Written operating procedures;
2. IRB membership rosters;
3. IRB member files including documentation of appointments, experience, education/training, and expertise;
4. IRB correspondence including reports to regulatory agencies;
5. IRB Protocol Files (See Section 14.2);
6. Convened IRB meeting minutes;
7. Documentation of review by an external IRB, when appropriate;
8. Documentation of IRB reliance and cooperative review agreements;
9. Documentation of independent or external investigator agreements;
10. Federal Wide Assurances;
11. Federal IRB Registrations; and
12. Documentation of complaints and any related findings and/or resolution.

### **14.2 IRB Protocol Files**

The IRB maintains a separate file for each protocol (including expanded access), HUD, emergency use, or report it receives for review in IRBNet 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;
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. DHHS grant application
9. IRB reviewer forms and checklists
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. For research reviewed by the convened board these determinations are recorded in the minutes;
14. Documentation of all IRB review actions;
15. Notification of expiration of IRB approval to the investigator;
16. Notification of suspension or termination of research;
17. Letters to investigator informing them of IRB review outcomes;
18. IRB correspondence to and from investigators related to the protocol;
19. All other IRB correspondence related to the research;
20. For studies evaluating the safety or effectiveness of medical devices, documentation of the device determination (exempt, non-significant risk, significant risk);
21. Reports of unanticipated problems involving risk to subjects or others; and
22. Any statements of significant new findings provided to subjects.

### **14.3 The IRB Minutes**

Draft minutes of IRB meeting proceedings are written and available for review by the next regularly scheduled IRB meeting. Once reviewed and accepted by the members, the IO will be notified that the minutes are available for review in IRBNet. Changes may not be made to finalized minutes without re-review by the IRB to verify accuracy.

Minutes of IRB meetings must contain sufficient detail to show the following, as applicable:

1. Attendance:
  - a. Each member's full name.
  - b. Each member's representative capacity (scientist, non-scientist, member who represents the general perspective of research participants, unaffiliated).
  - c. The names of members who participated in the convened meeting via an alternative mechanism, such as telephone or video conferencing.
  - d. If a consultant is present at the convened meeting, the name of the consultant, and a brief description of the consultant's expertise, and documentation that the consultant did not vote with the IRB or EC on the study.
  - e. The names of non-members and guests, such as IRB or EC support staff, researchers, and study coordinators.
  - f. When an alternate member replaces a primary member, including the name of the alternate member.
  - g. The names of IRB or EC members who leave the meeting because of a conflict of interest along with the fact that a conflict of interest is the reason for the absence.

**Note:** 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.

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. Actions taken, including separate deliberations, actions, and votes for each submission undergoing review by the convened IRB;
5. Vote counts on these actions (Total Number Voting; Number voting for; Number voting against; Number abstaining; Number of those recused). When a member is recused due to conflict of interest, the name of the member and reason for the recusal will be noted;
6. Basis or justification for actions disapproving or requiring changes in research;
7. Summary of controverted issues and their resolution;
8. Approval period for initial and continuing reviews, including identification of research that warrants review more often than annually and the basis for that determination;
9. Risk determination for initial and continuing reviews, and modifications when the modification alters the prior risk determination;

10. Justification for deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document;
11. 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;
12. Study-specific findings supporting that that the research meets each of the required criteria when the requirements for documentation of consent are waived;
13. Study-specific findings supporting that the research meets each of the criteria for approval for vulnerable populations under any applicable Subparts;
14. Exempt/significant risk/non-significant risk device determinations and the basis for those determinations;
15. Determinations related to conflicts of interest and acceptance or modification of conflict management plans;
16. 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;
17. Review and determinations related to interim reports (e.g., unanticipated problems or safety reports, serious or continuing noncompliance, suspensions or terminations, etc.);
18. A list of research approved under expedited review procedures since the time of the last such report;
19. An indication that, when an IRB member or alternate has a conflicting interest (see Section 25.2) with the research under review, the IRB member or alternate was not present during the final deliberations or voting; and
20. Key information provided by consultants will be documented in the minutes or in a report provided by the consultant.

#### **14.4 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 MaineHealth.

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. 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. Physicians, nurses, and pharmacists are considered scientists;
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, adults with impaired decision-making capacity, and other vulnerable populations commonly involved in MaineHealth research;
7. Role on the IRB (Chair, Vice-Chair, etc.);
8. Voting status; and
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. Changes in IRB membership are reported to OHRP and FDA on the federal IRB registration within 90 days of the change.

#### **14.5 Documentation of Exemptions**

Documentation of verified exemptions consists of the reviewer's citation of a specific exempt category and written concurrence that the activity described in the investigator's request satisfies the conditions of the cited exempt category as detailed in Section 5.

#### **14.6 Documentation of Expedited Reviews**

IRB records for initial and continuing review by the expedited procedure must include the reviewer's verification that the study qualifies for expedited review including the specific permissible category(ies), documentation that the activity satisfies the criteria for approval, the period of approval, and any determinations required by the regulations, or by MaineHealth policy, 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;

## 6. Approving research involving subjects with impaired decision capability

### 14.7 Access to IRB Records

IRB protocol files are secured in IRBNet, and are stored on MaineHealth servers behind the firewall, with administrative access controlled by the IRB office. Likewise, investigators control access to investigator records in the electronic system. All other IRB records (e.g., membership rosters) are kept secure in a limited access file on MaineHealth's servers, locked filing cabinets or locked storage rooms.

Ordinarily, access to IRB records is limited to the IO, ORC Director, IRB Manager, ORC staff, IRB members, 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.

Records are accessible for inspection and copying by authorized representatives of federal regulatory agencies during regular business hours.

IRB member rosters are available online at [www.mmcri.org](http://www.mmcri.org), and are only provided upon request to regulatory agencies, accreditation bodies, and persons or offices within MaineHealth with a legitimate need (e.g., Legal Counsel etc.).

All other access to IRB records is limited to those who have legitimate need for them, as determined by the IO, ORC Director, or IRB Manager.

### 14.8 Record Retention

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

IRB records for research cancelled without participant enrollment will be retained for at least three (3) years after closure.

IRB minutes are retained until all of the studies that were reviewed at that meeting have been completed for at least three (3) years.

After the noted times, IRB records may be shredded or otherwise securely destroyed.

## **15 Obtaining Informed Consent from Research Subjects**

No investigator conducting research under the auspices of MaineHealth 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 (LAR) unless a waiver of consent has been approved by the IRB of record. Except as provided in Sections 15.10 and 15.11 of these procedures, informed consent must be documented using 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 subjects in research conducted under the auspices of MaineHealth. When the MaineHealth IRB is serving as the IRB of record for external sites or personnel, the below requirements may be adapted as appropriate based upon the local context where the research will occur (e.g., who may serve as a LAR, etc).

### **15.1 Basic Requirements**

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 MaineHealth HRPP. Investigators are required to obtain legally effective informed consent from a subject or the subject's LAR 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, discussing, 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 by an investigator and continuing through the completion of the research study. Investigators must have received the appropriate training and be knowledgeable about the study procedures, potential risks, anticipated benefits, and alternatives in order that they may appropriately describe the research and answer questions. 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; electronic interface, 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, 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 to be able to answer questions about the study including those regarding risks, procedures, and alternatives. The MaineHealth IRB application solicits information regarding who will obtain consent. This should also be noted on the delegation of authority log.

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

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

## **15.2 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 with appropriate authority to make decisions regarding the activities called for in the research or a legally authorized representative (LAR);
2. The informed consent process provides the prospective subject (or LAR/guardian) with sufficient opportunity to read the consent document, when applicable;
3. The informed consent process provides the prospective subject (or LAR/guardian) with the opportunity to ask questions and have them answered;
4. The informed consent process shall be sought under circumstances that provide the subject (or LAR/guardian) with sufficient opportunity to consider whether to participate;
5. The informed consent process shall be sought under circumstances that minimize the possibility of coercion or undue influence;
6. The informed consent information must be presented in language that is understandable to the subject (or LAR/guardian). To the extent possible, the language should be understandable by a person who is educated to 8<sup>th</sup> grade level and layman's terms shall be used in the description of the research. The IRB may require or allow different readability standards based upon the characteristics of the target subject population;
7. For subjects with [Limited English Proficiency](#) (LEP), informed consent must be obtained in a language that is understandable to the subject (or LAR/guardian). In accordance with this policy, the MaineHealth IRB requires that informed consent discussions include an MaineHealth-certified interpreter (exceptions may be approved by the IRB on a case-by-case basis) when the prospective subject does not understand the language of the

person who is obtaining consent, and, in most circumstances, that consent materials are translated;

8. 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 any entity (including the investigator, the sponsor, and MaineHealth employees or agents) are released from liability for negligence, or appear to be so released; and
9. The investigator is responsible for ensuring that each prospective subject is adequately informed about all aspects of the research and understands the information provided.

### **15.3 Legally Authorized Representative (LAR)**

A Legally Authorized Representative (LAR) is defined by [45 CFR 46.102\(c\)](#) and [21 CFR 50.3](#) as *“an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.”*

Who may serve as LAR is determined by state law. Maine law does not specifically address informed consent by LARs of incapacitated persons for participation in clinical research. Thus, the applicable guidelines for determining the most appropriate LAR for research are based upon the guidelines that apply in the clinical setting.

See Section 16.6 for specific discussion of research involving children, including parent or guardian permission requirements.

For legally incompetent adults who are unable to make medical decisions, a legal representative (court appointed guardian) or durable power of attorney for health care must provide informed consent for non-emergent medical treatment. The legal guardian must be authorized by the court to make decisions regarding the types of activities, procedures, or treatments called for in the research to serve as LAR. Substitute decision-makers, as defined in MaineHealth's clinical informed consent policy (*Informed Consent, MaineHealth Institutional Policy Manual [06/09/17]*), may serve as LAR for research involving clinical procedures or treatments when a court appointed guardian or durable power of attorney for health care are not in place.

When the MaineHealth IRB serves as the IRB of record for external sites and the use of LARs is proposed, information regarding relevant state law and local policy will be sought (local context information) and applied.

LARs should be well informed regarding their roles and responsibilities when asked to provide surrogate consent. In addition to the consent information, LARs should be informed that their obligation is to try to determine what the potential subject would do if able to provide consent, or if the potential subject's wishes cannot be determined, what they think is in the person's best interest.

Investigators must describe the intended use of LARs in their submission to the IRB. The IRB determines whether the use of LARs is appropriate for a given research study.

Further discussion and procedures for assessment of capacity and inclusion of adults with impaired decision-making capacity in research are described in Section 16.7.

#### 15.4 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. Contact information for the research team for questions, concerns, or complaints
8. Contact information for someone independent of the research team for problems, concerns, questions, or input
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. For **FDA-regulated studies**, a statement that notes the possibility that the Food and Drug Administration may inspect the records;
11. 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.”

### **15.5 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. When applicable, the amount and schedule of all payments
5. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
6. 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;
7. The approximate number of subjects involved in the study.

### **15.6 Subject Withdrawal or Termination**

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 plans and consent documents.

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

1. 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. This should be disclosed in the consent; or
2. For research not subject to FDA regulations: The investigator should inform subjects whether the investigator or study sponsor intends to either: (1) retain and analyze already collected data relating to the subject up to the time of subject withdrawal; or (2) honor a research subject's request that the investigator or study sponsor will destroy the subject's data or that the investigator or study sponsor will exclude the subject's data from any analysis.

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 participate in 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.

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.

### **15.7 Documentation of Informed Consent**

Except as provided in Sections 15.10 and 15.11 of this document, informed consent must be documented by the use of a written consent form approved by the IRB.

1. Informed consent is documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's LAR at the time of consent;
2. For research conducted in accordance with ICH-GCP E6 or in facilities subject to Joint Commission requirements, the name of the person who obtained consent and the date they did so is documented on the written consent form;
3. 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. When appropriate, a copy of the consent form is uploaded into the electronic health record;

The consent form may be either of the following:

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

A short form written consent document stating that the elements of informed consent have been presented orally to the subject or the subject's LAR. When this method is used:

- a. The oral presentation and the short form written document should be in a language understandable to the subject; and
- b. There must be a witness to the oral presentation; and
- c. The IRB must approve a written summary of what is to be said to the subject (the approved full consent document may serve as this summary); and
- d. The short form document is signed by the subject;

- e. The witness must sign both the short form and a copy of the summary; and
- f. The person actually obtaining consent must sign a copy of the summary; and
- g. A copy of the summary must be given to the subject or representative, in addition to a copy of the short form.
- h. When the short form procedure is used with subjects who do not speak or read English, or have [Limited English Proficiency](#) (LEP), (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; (iii) the witness should be fluent in both English and the language of the subject. The witness to the consent process may be a member of the study team (in addition to the person obtaining consent); iv) for research subject to FDA regulation, FDA expects that the subject will be provided with a fully translated consent document as soon as possible.

The MaineHealth IRB has reviewed and approved the content of a template short form, and all translations of it.

## **15.8 Special Consent Circumstances**

### **15.8.1 Enrollment of persons with Limited English 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 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, as applicable. Generally, translated consent forms should not be prepared until the final approved version of the English-language version is available. To ensure that translated documents are accurate, the IRB may choose to require a certified translation, or have an independent back-translation.
- 2. Unexpected enrollment:** If a person who does not speak or read, or has limited proficiency in, English unexpectedly 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 or legally effective.

If an investigator decides to enroll a subject into a study for which there is not an existing 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 15.7.

**3. Use of interpreters in the consent process:** An MaineHealth-certified interpreter (i.e., not a family member) should assist in presenting information and obtaining informed 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. 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.

#### **4. Braille consent**

For blind subjects who read Braille, the IRB may approve a consent document prepared in Braille. To ensure 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 15.8.3).

#### **15.8.2 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 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 15.7.

#### **15.8.3 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 15.10.

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 that the subject gave oral consent or made their mark. 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 video-tape.

#### **15.8.4 Physically-Challenged Subjects**

A person who is physically challenged (e.g., physically unable to talk or write) can enroll in research if competent and able to indicate voluntary consent to participate. Whenever possible, the subjects should sign the consent form or make their mark by initialing or making an X. As with oral consent, a witness to the consent process is recommended and the circumstances and consent process should be carefully documented in the research records.

#### **15.8.5 Remote Consent Process**

The IRB may approve a process that allows the informed consent document to be delivered by an electronic platform (e.g., computer, tablet, smartphone), mail or facsimile to the potential subject or the potential subject's legally authorized representative and to conduct the consent interview by telephone or video consult. All other applicable conditions for documentation of informed consent must also be met when using this procedure.

### **15.9 Waiver or Alteration 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 waives 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.

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.

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

Waivers of consent are not permissible under either option for federally-funded research using Newborn Dried Blood Spots.

### **15.10 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 **either** that:

1. The only record linking the subject and the research would be the consent document 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). Subjects must 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.

OR

2. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Procedures such as non-sensitive surveys, questionnaires and interviews generally do not require written consent when conducted by non-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.)

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.

### **15.11 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 research that is not FDA-regulated.

The FDA exception from informed consent requirements for emergency research under FDA regulations 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 this section. The DHHS waiver is not applicable to research involving prisoners, pregnant women, fetuses, or in vitro fertilization.

### **15.11.1 Definitions**

**Planned Emergency Research.** 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.

### **15.11.2 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:
  - a. The subjects will not be able to give their informed consent as a result of their medical condition;
  - b. The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
  - c. 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:
  - a. Subjects are facing a life-threatening situation that necessitates intervention;
  - b. 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

- c. 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.
7. Additional protections of the rights and welfare of the subjects will be provided, including, at least:
  - a. 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;
  - b. 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;
  - c. 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;
  - d. Establishment of an independent data monitoring committee to exercise oversight of the research; and
  - e. 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.

#### **15.11.2.1 FDA-regulated Planned Emergency Research**

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 15.11.2 are satisfied.

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 such investigations may not be submitted as amendments under [312.30](#) or [812.35](#).

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.

The IRB determinations and documentation required in this section 15.11 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\(b\)](#).

### **15.11.2.2 Documentation and Reporting of Planned Emergency Research Not Subject to FDA Regulations**

The IRB responsible for the review, approval, and continuing review of the research must approve both the research and a waiver of informed consent and have (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 15.11 have been met relative to the research.

## 16 Vulnerable Subjects in Research

When participants in research conducted under the auspices of MaineHealth 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 subjects are met and that appropriate additional protections for vulnerable subjects are in place.

### 16.1 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 [[45 CFR 46.402\(a\)](#)].

According to Maine State Law, minors are persons under the age of eighteen. The general rule is that a person may sign legally-binding agreements and consent for his or her own medical care at the age of eighteen. Therefore, MaineHealth IRB defines children as persons who are under eighteen years of age. However, a minor may give consent to all medical, mental, dental and other counseling and services if the minor: 1) has been living separately from parents or legal guardians for at least 60 days and is independent of parental support; 2) Is or was legally married; 3) Is or was a member of the Armed Forces of the United States; or (4) Has been emancipated by the court pursuant to 22 M.R.S.A §3506-A (22 M.R.S.A. §1503). Furthermore, Maine law also permits minors to seek care for drug addiction, sexually transmitted diseases, emotional disorders, or abortion or mental health treatment without parental or guardian permission (Title 22 M.R.S.A. §1502). However, if hospitalization of greater than 16 hours is required for treatment, consent is required (Title 22 M.R.S.A §1823). Because Maine statutes do not specifically address consent for research, MaineHealth IRB will review issues of actual consent (as opposed to assent) related to the enrollment of minors (as defined under 22 M.R.S.A §1503) in research on a case-by-case basis.

**NOTE:** For research conducted in jurisdictions other than Maine, the research must comply with the laws regarding the legal age of consent in the relevant jurisdictions. Legal counsel will be consulted with regard to the laws in other jurisdictions or such “local context” information will be sought through other mean (e.g., according to the terms of a reliance agreement).

**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 [[45 CFR 46.402\(e\)](#)].

In Maine, a “Guardian” of a minor (known as the guardian’s “ward”) means a person that has accepted a court or testamentary guardian appointment (18-A M.R.S.A. §5-201 and §5-203) and has the powers and responsibilities of a parent who has not been deprived of custody of a minor and unemancipated child, except that a guardian is not legally obligated to provide from the guardian’s own funds for the ward and is not liable to 3<sup>rd</sup> persons by reason of the parental relationship for act of the ward. The guardian is empowered to act in the minor’s best interests and may facilitate the ward’s education, social or other activities and give or withhold consents

or approvals related to medical, health or other professional care, counsel, treatment or services for the ward. (18-A M.R.S.A. §5-209).

**NOTE:** For research conducted in jurisdictions other than Maine, the research must comply with the laws regarding guardianship in all relevant jurisdictions. Legal counsel will be consulted with regard to the laws in other jurisdictions or such “local context” information will be sought through other means (e.g., according to the terms of a reliance agreement).

**Fetus.** A fetus means the product of conception from implantation until delivery [[45 CFR 46.202\(c\)](#)].

**Dead fetus.** A fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord [[45 CFR 46.202\(a\)](#)].

**Delivery.** Delivery means complete separation of the fetus from the woman by expulsion or extraction or any other means [[45 CFR 46.202\(b\)](#)].

**Neonate.** A neonate is a newborn [[45 CFR 46.202\(d\)](#)].

**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 [[45 CFR 46.202\(h\)](#)]. If a neonate is viable, then, for the purposes of participation in research, the neonate is considered a child and the rules regarding participation of children in research apply.

**Nonviable neonate.** A nonviable neonate means a neonate after delivery that, although living, is not viable [[45 CFR 46.202\(e\)](#)].

**Pregnancy.** 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 [[45 CFR 46.202\(f\)](#)].

**Prisoner.** Prisoner means 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 [[45 CFR 303\(c\)](#)].

## **16.2 Involvement of Vulnerable Populations in Research**

When 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. When the IRB does not have the relevant expertise among its membership, expertise may be sought through the use of consultants.

45 CFR 46 has additional subparts designed to provide extra protections for certain defined 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 regulated by the FDA includes equivalent protections and obligations when **research** involves children ([Subpart D](#)). Research conducted, supported, or otherwise regulated by other federal agencies may or may not be covered by the subparts.

In its FWA, MaineHealth 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.

### **16.3 Procedures**

The following policies and procedures apply to all research involving vulnerable populations under the oversight of the MaineHealth IRB regardless of funding. Subsequent sections address additional procedures and requirements that apply to specific populations.

#### **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. IRB staff, in collaboration with the IRB Chair as needed, ensure that the IRB has the relevant expertise with the vulnerable population, and, if necessary, arrange for consultation. When the research involves no more than minimal risk and is eligible for expedited review, the designated reviewer may determine the need for additional expertise to ensure the protection of the vulnerable population(s);
4. The IRB evaluates the proposed safeguards, including, if applicable, the proposed plans for identifying, recruiting, and obtaining consent from subjects or their legally authorized representatives and the plans for assent of children and adults unable to provide consent;
5. When applicable, the IRB considers any costs associated with participation in the proposed research and any plans for reimbursement of expenses or provision of compensation, and the potential impact of such on the vulnerable population(s);

6. The IRB evaluates the research to determine whether the proposed plan is adequate or if additional protections are needed such as interim monitoring, review more than annually, or the use of a data and safety monitoring board, consent monitor, or research subject advocate.

### **Modifications to Research**

1. When an investigator proposes to add inclusion of a vulnerable population after research has already been approved by the IRB, the investigator must submit a modification request to the IRB identifying the population they would like to add, justification for inclusion of the population, and any modifications to the research plan to ensure protection of the subjects' rights and welfare;
2. The IRB staff and IRB will follow the procedures outlined for initial review above.

### **Continuing Review**

1. 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. When research does not include any interaction or intervention with subjects, and such information is not gathered, this should be noted on the continuing review report;
2. IRB staff, in collaboration with the IRB Chair as needed, ensure that the IRB has the relevant expertise with the vulnerable population, and, if necessary, arrange for consultation. When the research involves no more than minimal risk and is eligible for expedited review, the designated reviewer may determine the need for additional expertise to ensure the protection of the vulnerable population(s);
3. The IRB reviews the continuing review information, and any relevant information reported to the IRB during the period of approval, and determines whether the inclusion of vulnerable populations and the plans to protect the rights and welfare of vulnerable subjects remains appropriate.

## **16.4 Research Involving Pregnant Women, Human Fetuses and Neonates**

The following applies to all research involving pregnant women, human fetuses, and neonates reviewed by the MaineHealth IRB. DHHS-specific requirements are noted in the appropriate sections.

If a woman becomes pregnant while participating in a study that has not been approved for inclusion of pregnant women, the IRB must be notified immediately so that the IRB can determine whether the subject may continue in the research, whether additional safeguards are needed, and to make the determinations required by the regulations and these policies.

## 16.4.1 Research Involving Pregnant Women or Fetuses

### 16.4.1.1 Research Not Conducted or Supported by DHHS

For research not conducted or supported by DHHS, where the risk to the pregnant women and fetus is no more than minimal, no additional safeguards are required by policy and there are no restrictions on the involvement of pregnant women in research. However, the IRB may determine that additional safeguards or restrictions are warranted for a specific study.

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 16.1) 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. The IRB may allow individuals whose normal responsibilities include determining the viability of fetuses to be engaged in the research, if their involvement in the determination of viability for an individual fetus cannot be avoided. 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 involving the subject(s) in 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 5 business days. The circumstances that prohibited prospective confirmation of viability and the outcome of the subsequent consultation will be reported to the IRB within 10 business days.

#### **16.4.1.2 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 16.1) who are pregnant, assent and permission are obtained in accord with the provisions of permission and assent in Section 16.6.2;
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.

## **16.4.2 Research involving Neonates of Uncertain Viability or Nonviable Neonates**

### **16.4.2.1 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 conditions listed below are met. The IRB will determine on a case-by-case basis whether safeguards or restrictions should be required for minimal risk research.

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 involving the subject(s) in 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 5 business days. The circumstances that prohibited prospective confirmation of viability and the outcome of the subsequent consultation will be reported to the IRB within 10 business days.
4. The requirements of Neonates of Uncertain Viability or Nonviable Neonates (see below) have been met as applicable.

**Neonates of Uncertain Viability.** Until it has been ascertained whether 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 LAR is obtained in accord with the provisions of permission and assent, except that the consent of the father or his LAR 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 LAR of either or both of the parents of a nonviable neonate will not suffice.

#### **16.4.2.2 Research Conducted or Supported by DHHS**

Neonates of uncertain viability and nonviable neonates may be involved in research conducted or supported by DHHS 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) have been met as applicable.

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

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

1. The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and
2. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's LAR is obtained in accord with the provisions of permission and assent, except that the consent of the father or his LAR 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 LAR of either or both of the parents of a nonviable neonate will not suffice.

#### **16.4.3 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 research regulations and MaineHealth policies).

#### **16.4.4 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.

## **16.4.5 Research Not Otherwise Approvable**

### **16.4.5.1 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 provisions described previously in this section, 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 requirements for informed consent described in this manual.

### **16.4.5.2 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.

## **16.5 Research Involving Prisoners**

### **16.5.1 Applicability**

While MaineHealth does not plan to engage in research involving prisoners, these procedures would be followed in the event a subject became a prisoner.

For research not conducted or supported by DHHS, where the risk to prisoners is no more than minimal (as defined in Section 16.5.2), no additional safeguards are required under these policies and procedures. However, the IRB may determine that additional safeguards or restrictions are warranted for a specific study.

For research involving more than minimal risk, and for research conducted or supported by DHHS, the requirements outlined in this section apply.

As applicable, investigators must obtain permission from and abide by the requirements of correctional authorities and state or local law.

### **16.5.2 Minimal Risk**

Minimal risk, in studies involving prisoners, means the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

### **16.5.3 Composition of the IRB**

In addition to satisfying the general membership requirements detailed in other sections of these policies and procedures, when reviewing research involving prisoners, the IRB must also meet the following requirements:

1. A majority of the IRB (exclusive of prisoner members) must have no association with the prison(s) involved, apart from their membership on the IRB;
2. At least one member of the IRB must be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one IRB, only one IRB need satisfy this requirement; and
3. The prisoner representative must be a voting member of the IRB. A comment may be added to the roster indicating that the prisoner representative will only count towards quorum when s/he is in attendance and reviewing studies involving prisoners.

### **16.5.4 Review of Research Involving Prisoners**

#### **Initial Review of Research Proposal**

1. The prisoner representative must review research involving prisoners, focusing on the requirements outlined in Subpart C and these policies;
2. The prisoner representative must receive all review materials pertaining to the research (same as primary reviewer); and
3. The prisoner representative must be present at a convened meeting when the research involving prisoners is reviewed. If the prisoner representative is not present, research involving prisoners cannot be reviewed or approved. The prisoner representative may attend the meeting by phone, video-conference, or webinar, so long as the representative is able to participate in the meeting as if they were present in person at the meeting.
4. The IRB must be familiar with the specific conditions in the local prison(s) or jail site(s) that are pertinent to subject protections, before approving the proposal for the local site ([45 CFR 46.107\(a\)](#)).

#### **Modifications to Research**

1. Minor modifications to research involving prisoners may be reviewed using the expedited procedure described below;

2. Modifications reviewed by the convened IRB must use the same procedures for initial review including the responsibility of the prisoner representative to review the modification and participate in the meeting (as described above).

### **Continuing Review**

1. Continuing review will follow the same procedures as initial review including the responsibility of the prisoner representative to review the continuing review materials and participate in the meeting (as described above).

### **Expedited Review**

1. Research **involving interaction** with prisoners may be reviewed by the expedited procedure if a determination is made that the research involves no greater than minimal risk for the prison population being studied and the research falls within the categories of research eligible for expedited review. Whenever possible, the prisoner representative will be consulted to verify that they agree that the research is minimal risk and to conduct (if designated by the IRB Chair as an expedited reviewer) or participate in the expedited review as a consultant. Review of modifications and continuing review will follow these same procedures;
2. Research **that does not involve interaction** with prisoners (e.g., records review) may be reviewed by the expedited procedure if a determination is made that the research involves no greater than minimal risk for the prison population being studied. Review by a prisoner representative is not required. The prisoner representative may review the research as a reviewer (if designated by the IRB Chair as an expedited reviewer) or consultant. Review of modifications and continuing review will follow these same procedures.

### **16.5.5 Incarceration of Enrolled Subjects**

1. If a subject becomes a prisoner while enrolled in a research study that was not reviewed according to these procedures, the investigator must promptly notify the IRB and the IRB shall:
  - a. Confirm that the subject meets the definition of a prisoner;
  - b. Consult with the investigator to determine if it is in the best interests of the subject 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 that should continue until the IRB is able to review the research applying the standards and requirements for research involving prisoners.
2. If the subject should continue, one of two options are available:
  - a. Keep the subject enrolled in the study and review the research applying the standards and requirements for research involving prisoners. If some of the requirements 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

subject to remain in the study, keep the subject enrolled and, if the research is DHHS-conducted or supported, inform OHRP of the decision along with the justification; or

- b. Remove the subject from the study and keep the subject on the study intervention under an alternate mechanism such as compassionate use or off-label use.
3. If a subject 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 involving the prisoner subject to take place during the temporary incarceration), keep the subject enrolled.
  - b. If the temporary incarceration has an effect on the study, follow the guidance outlined above.
4. If a subject becomes incarcerated while enrolled in a study, the IRB may determine that follow up data may be collected for the incarcerated participant.

#### **16.5.6 Additional Duties of the IRB**

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

1. The research falls into one of the following **permitted categories** [[45 CFR 46.306\(a\)\(2\)](#)]:
  - a. Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
  - b. Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
  - c. 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;
  - d. 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; or

- e. The research qualifies under the HHS Secretarial waiver that applies to certain epidemiological research ([68 FR 36929, June 20, 2003](#)). 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.
2. Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;
3. The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers;
4. Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the 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 proposal;
5. The information is presented in language which is understandable to the subject population;
6. Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and
7. Where the IRB finds there may be a need for follow-up examination or care of 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.

#### **16.5.7 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, MaineHealth 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 MaineHealth on behalf of the Secretary.

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:

1. The IRB-approved protocol; any relevant DHHS grant application or proposal;
2. Any IRB application forms required by the IRB; and
3. 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:

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

## **16.6 Research Involving Children**

The following applies to research involving children, (with the exception of MaineHealth Flex Categories for non-federally funded research-See Section 12.1.2 for allowable expedited categories).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.

### **16.6.1 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. **Research/Clinical Investigations not involving greater than minimal risk** [[45 CFR 46.404/21 CFR 50.51](#)]. 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 16.6.2.

2. Research/Clinical Investigations involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects [[45 CFR 46.405/21 CFR 50.52](#)]. 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:
  - a. The risk is justified by the anticipated benefit to the subjects;
  - b. The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative options; and
  - c. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 16.6.2.
3. 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 [[45 CFR 46.406/21 CFR 50.53](#)]. 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:
  - a. The risk represents a minor increase over minimal risk;
  - b. The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
  - c. The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
  - d. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 16.6.2.
4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate serious problems affecting the health or welfare of children [[45 CFR 46.407/21 CFR 50.54](#)]. 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:

- a. DHHS-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.
- b. FDA-regulated research in this category will be referred for review by the Commissioner of Food and Drugs.
- c. 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:
  - i. That the research in fact satisfies the conditions of the previous categories, as applicable; or
  - ii. The following:
    - 1. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
    - 2. The research will be conducted in accord with sound ethical principles; and
    - 3. Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in Section 16.6.2.

## **16.6.2 Parental Permission and Assent**

### **16.6.2.1 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 15.

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.

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

1. The research meets the provisions for waiver in Section 15.10; or
2. For research that is not FDA-regulated, 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.

Permission from parents or legal guardians must be documented in accordance with and to the extent required by Section 15.7.

#### **16.6.2.2 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 is also responsible for determining whether and how assent must be documented.

To document assent, some IRBs require the use of an assent form while some do not. The MaineHealth IRB prefers that the investigator document each child's assent on the permission form signed by their parent(s); the IRB prefers that investigators not use a separate form. The abilities and needs of children vary widely and investigators should provide the information in a format tailored to the child in front of them. In many cases, assent forms are simplified consent forms that include elements that are irrelevant to assent (e.g. risk assessment, confidentiality) and are rarely written with sufficient simplicity of style and readability to achieve their intended objective.

The MaineHealth IRB does not require children to sign their name to document their assent. On the MaineHealth template consent/permission form signature pages, the signature of the child is left optional. MaineHealth's preference is for investigators to focus on the assent process rather than on obtaining a signature for a form. The child's decision regarding whether or not to assent to participation in the research should be documented in the child's research record by the person obtaining assent.

The MaineHealth IRB may determine that the assent process be witnessed by an individual not affiliated with the study team or child's family. The witness may sign the consent form attesting to the assent of the child.

### **16.6.2.3 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 16.6.1), **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.

## **16.7 Adults with Impaired Decision-Making Capacity**

When vulnerable populations are included in research, regulations require that additional safeguards are put in place to protect the rights and welfare of these subjects. [\[45 CFR 46.111\(b\)/21 CFR 56.111\(b\)\]](#) Adults who lack or who have impaired, fluctuating, or diminishing decision-making capacity (collectively referred to as “adults with impaired decision-making capacity” in this section) are particularly vulnerable. Investigators and IRBs must carefully consider whether inclusion of such subjects in a research study is appropriate; and when it is, must consider how best to ensure that these subjects are adequately protected. The principals and procedures outlined in this section are intended to assist MaineHealth investigators and the IRB with the development and review of research involving adults with impaired decision-making capacity.

### **16.7.1 Informed Consent**

Obtaining legally effective informed consent before involving human subjects in research is one of the central ethical principles described in the Belmont Report and provided for by federal regulations governing research.

As discussed previously, the informed consent process involves three key features: (1) providing the prospective subject the information needed to make an informed decision (in language understandable to him or her); (2) facilitating the understanding of what has been disclosed; and (3) promoting the voluntariness of the decision about whether to participate in the research.

Among other requirements, for consent to be legally effective, the potential subject or their LAR must have the necessary decision-making capacity to make a rational and meaningful choice about whether to participate (or continue participating) in a study.

### **16.7.2 Decision-Making Capacity**

“Decision-making capacity” refers to a potential subject’s ability to make a rational and meaningful decision about whether or not to participate in a research study. This ability is generally thought to include at least the following four elements:

1. Understanding, i.e., the ability to comprehend the disclosed information about the nature and purpose of the study, the procedures involved, the risks and benefits of participating versus not participating, and the voluntary nature of participating;
2. Appreciation, i.e., the ability to appreciate the significance of the disclosed information and the potential risks and benefits for one’s own situation and condition;
3. Reasoning, i.e., the ability to engage in a reasoning process about the risks and benefits of participating versus alternatives, and;
4. Choice, i.e., the ability to express a choice about whether or not to participate.

“Decision-making capacity” should not be confused with the legal concept of “competence.” While the court may consider information about a person’s decision-making capacity in making a competency determination, the terms are not synonymous. Incompetence is a legal determination made by a court of law. For example, someone who is judged legally incompetent to manage their financial affairs may retain sufficient decision-making capacity to make meaningful decisions about participating in a research protocol. Likewise, people who have normal cognitive functioning and are considered legally competent may be put into circumstances where their decision-making capacity is temporarily impaired by a physical or mental condition or by alcohol or drugs.

Decision-making capacity is protocol and situation-specific. Thus, a person may have capacity to consent to participate in low risk research in usual circumstances, but not have the capacity to consent to a higher risk protocol when s/he is under significant stress or faced with unfamiliar circumstances.

### **16.7.3 Inclusion of Adults with Impaired Decision-Making Capacity in Research**

Research involving adult 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.

Investigators must disclose to the IRB both plans and justification for including adults with impaired decision-making capacity in a given research proposal. If adults with questionable or fluctuating capacity will be included, investigators must specify procedures for assessing capacity prior to providing informed consent and, if appropriate, for re-evaluating capacity during study participation. If a prospective subject’s capacity to consent is expected to diminish, the investigator should consider requesting that the subject designate a future LAR prior to enrollment in the research, including the future LAR in the initial consent process, and obtaining written documentation of the subject’s wishes regarding participation in the research. When the study includes subjects likely to regain capacity to consent while the research is ongoing,

the investigator should include provisions to inform them of their participation and seek consent for ongoing participation.

Plans for evaluation of capacity should be tailored to the subject population and the risks and nature of the research. In some instances, assessment by a qualified investigator may be appropriate. However, an independent, qualified assessor should evaluate subjects' capacity when the risks of the research are more than a minor increase over minimal or the investigator is in a position of authority over a prospective subject. The person(s) evaluating capacity must be qualified to do so and may use appropriate tools and. Assessments of capacity should be documented in the research record, and when appropriate, in the medical record.

Under some circumstances, it may be possible for investigators to enable adults with a degree of decisional impairment to make voluntary and informed decisions to consent, assent, or refuse participation in research. Potential measures include repetitive teaching, 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 discussions, use of waiting periods to allow more time for the potential subject to consider the information that has been presented, or involvement of a trusted family member or friend in the disclosure and decision-making process. Audio or videotapes, electronic presentations, or written materials used to promote understanding must be provided to the IRB for review and approval prior to use.

When a prospective subject is deemed to lack capacity to consent to participate in research, investigators may obtain informed consent from the individuals' surrogate or LAR (See Section 15.3). Under these circumstances, the prospective subject should still be informed about the research in a manner compatible with the subjects' likely understanding and, if possible, be asked to assent to participate. Potential subjects who express resistance or dissent (by word, gesture, or action) to either participation or use of surrogate consent, should be excluded from the study. Some subjects may initially assent but later resist participation. Under no circumstances may an investigator or caregiver override a subject's dissent or resistance. 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, how assent will be documented, and a copy of the assent form (as applicable). 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.

When inclusion of adults with impaired decision-making capacity is **not anticipated** and a plan for inclusion of such subjects **has not been** reviewed and approved by the IRB, and an enrolled subject becomes unable to provide consent or impaired in decision-making capacity, the investigator is responsible for promptly notifying the IRB (as soon as possible but within 5 business days). The investigator should consider whether continuing participation is appropriate and, if so, present a plan for surrogate consent from a LAR and, if appropriate, a plan to periodically evaluate capacity and re-obtain consent if possible.

#### 16.7.4 IRB Review

The IRB review process will include at least one member, or a consultant, who is experienced with or otherwise knowledgeable about the population when the research involves greater than minimal risk, or the research is minimal risk but includes interactions with subjects, and the proposed subject population includes adults with impaired decision-making capacity.

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 adults with impaired decision-making capacity, the IRB should consider whether any components of the research involve risks that are greater for participants with diminished capacity. For example, whether subjects 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 should consider the following in evaluating research involving adults 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 whether 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 periodic re-evaluation of capacity and/or periodic re-consent should be required; and
13. Whether a research subject advocate or consent monitor should be required, for some or all subjects.

In general, the IRB will only approve research involving subjects unable to provide consent or with impaired decision-making capacity when the aims of the research cannot reasonably be achieved without inclusion of the population, and there are appropriate provisions to: (1) evaluate capacity, (2) obtain consent (and assent if possible), and (3) otherwise protect subjects.

## 17 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 investigations of investigational drugs and biological products must be conducted according to FDA's IND regulations, [21 CFR Part 312](#), and other applicable FDA regulations. Evaluations of the safety or effectiveness of a medical device must be conducted according to FDA's IDE regulations, [21 CFR Part 812](#), and other applicable FDA regulations.

The following procedures describe the review of FDA-regulated research by the MaineHealth IRB.

### 17.1 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.

**Clinical Investigation.** Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies. [[21 CFR 50.3\(c\)](#)]

**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. [[21 U.S.C. 321\(ff\)](#)]

**Emergency Use.** Emergency use is defined as the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval. [[21 CFR 56.102\(d\)](#)]

**Humanitarian Use Device (HUD).** A Humanitarian Use Device is a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year.

**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\(a\)](#)]

**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.

**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. [[21 CFR 812.3\(m\)](#)]

## 17.2 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\(d\)](#)]

### 17.3 Investigator Responsibilities

The investigator holds additional responsibilities when conducting a clinical investigation subject to FDA regulations. These responsibilities include, but are not limited to, the following:

1. The investigator is responsible for indicating on the IRB application that the proposed research is FDA-regulated and for providing relevant information regarding the test article.
2. 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 FDA or IRB.
3. The investigator is responsible for personally conducting or supervising the investigation. When 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.
4. 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 or sponsor), and identify the dates of involvement in the study. An investigator should maintain separate lists for each study conducted by the investigator.
5. The investigator is responsible for protecting the rights, safety, and welfare of subjects under their care during a clinical trial. This responsibility includes:
  - a. Informing subjects that the test article is being used for investigational purposes and ensuring that the requirements relating to obtaining informed consent are met
  - b. Providing or arranging for 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
  - c. 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)
  - d. Adhering to the protocol so that study subjects are not exposed to unreasonable risks
  - e. 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.

6. 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.
7. 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, but are not limited to: 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. For clinical investigations of medical devices, required records must be maintained for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. Other regulations, such as HIPAA, organizational policies, or contractual agreements with sponsors may necessitate retention for a longer period of time.
8. The investigator is responsible for controlling test articles according to FDA regulations and the Controlled Substances Act, if applicable.
9. For research reviewed by the MaineHealth IRB, 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 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. Investigational drugs and devices must be labeled in accordance with federal and state standards.
  - d. All devices received for a study must be stored in a locked environment under secure control with limited access. When applicable, 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.
10. 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.

11. 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.

#### **17.4 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 the research requires an IND. Applications should provide detail consistent with that expected on a drug protocol 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.

#### **17.5 Clinical Investigations of Articles Regulated as Drugs or Devices**

##### **17.5.1 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 or device under FDA regulations, the investigator must indicate on the IRB application whether 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;
2. Letter/communication from FDA;
3. Letter/communication from industry sponsor; or
4. Other document and/or communication verifying the IND/IDE.

For investigational devices, the study may be exempt from IDE requirements (IDE-exempt) 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 IDE-exempt or NSR, then the investigator should include documentation with the submission providing the basis for IDE-exempt or NSR categorization for the IRB's consideration. If the FDA has determined that the device as used in the study is IDE-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 IDE-exempt or NSR; or,
3. If neither of the above applies, the IRB will determine that an IND is necessary, or that a device study is exempt or NSR, or must be submitted to the FDA for an IDE or for a determination, 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.

### **17.5.2 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](#)].

Please Note: FDA has provided specific [guidance](#) for evaluating whether this exemption applies to studies of marketed drugs/biologics for the treatment of cancer.

- 2. For clinical investigations involving defined (blood grouping serum, reagent red blood cells, and anti-human globulin) in vitro diagnostic biological products, 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](#)
- 3. A clinical investigation involving use of a placebo is exempt from the requirements of part 312 if the investigation does not otherwise require submission of an IND.
- 4. 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\(d\)\(3\)](#)].
- 5. 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.
6. FDA practices enforcement discretion for research using cold isotopes of unapproved drugs if all of the following conditions are met:
- e. 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;
  - f. The research is not intended for immediate therapeutic, diagnostic, or preventive benefit to the study subject;
  - g. 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;
  - h. The quality of the cold isotope meets relevant quality standards; and
  - i. The investigation is conducted in compliance with the requirements for IRB review and informed consent. [21 CFR parts [56](#) and [50](#), respectively]

### **17.5.3 Investigational Device Exemptions**

For clinical investigations of medical 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.

#### **17.5.4 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:

1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
2. 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;
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.

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 17.5.1. 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 IDEs, 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):
  - a. Labels the device in accordance with [812.5](#);
  - b. 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;
  - c. 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 the requirement is waived by the IRB;
  - d. Complies with the requirements of [812.46](#) with respect to monitoring investigations;
  - e. 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 \(10\)](#);
  - f. 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
  - g. 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.

## **17.6 Diagnostic or Treatment Use of 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 an IRB 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.

### **17.6.1 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 or entity that obtains approval of an HDE from the FDA.

### **17.6.2 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.

### **17.6.3 Procedures**

The relevant requirements and procedures for research 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 MaineHealth facilities 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, organizational 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;

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 consent process; and
6. Other relevant materials (e.g., training certificates) as identified in the Application Form

The IRB will review the 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. Proposed changes may be submitted using the Research Application/Amendment Wizard Form and should be accompanied by any revised materials or supporting documentation. 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 those ordinarily required for continuing review, as well as:

1. The most recent periodic report to the FDA by the HDE holder;

2. The current patient information packet, if applicable;
3. The current consent, if applicable;
4. Other materials as identified on the Progress report, Study completion, and RNI form, or supplemental forms
5. Any other new relevant information or materials

The IRB may conduct continuing review using expedited review procedures or review by the convened IRB.

#### **17.6.4 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 MaineHealth IRB Chair including the identification of the patient involved, the date of the use, and the reason for the use. [\[21 CFR 812.124\]](#)

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.

#### **17.7 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 the use of investigational or unapproved/uncleared medical products (all referred to as "investigational" throughout this section) outside of a clinical trial, where the primary intent is treatment, rather than research. Because the 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 LAR and to monitor for safety.

Charging for expanded access use of investigational products is discussed in Section 17.8.

### 17.7.1 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 for patients with serious or immediately life-threatening diseases or conditions who lack other therapeutic options and may benefit from the investigational agent. Expanded access is sometimes referred to as compassionate use or treatment use.

For the purposes of expanded access to investigational drugs, ***immediately life-threatening disease or condition*** means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. ***Serious disease or condition*** means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. [[21 CFR 312.300\(b\)](#)]

Expanded access may also apply to (1) situations when a drug has been withdrawn for safety reasons, but there exists a patient population for whom the benefits of the withdrawn drug continue to outweigh the risks; (2) use of a similar, but unapproved drug (e.g., foreign-approved drug product) to provide treatment during a drug shortage; (3) use of an approved drug where availability is limited by a risk evaluation and mitigation strategy (REMS); and (4) use for other reasons. All are referred to as "investigational" for the purposes of these SOPs.

Under the FDA's expanded access rule, access to investigational drugs for treatment purposes is available to:

- Individual patients, including in emergencies [[21 CFR 312.310](#)]
- Intermediate-size patient populations [[21 CFR 312.315](#)]
- Widespread use under a treatment protocol or treatment IND [[21 CFR 312.320](#)]

The following section addresses expanded access for individual patients. Investigators seeking expanded access for intermediate-size populations or widespread use should consult with the ORC Office. Convened IRB review is generally required for intermediate or widespread expanded access unless the FDA has issued a waiver.

Physicians seeking access to investigational drugs under expanded access should work closely with the sponsor or manufacturer, the FDA, and the ORC, to determine the appropriate access mechanism and ensure that proper regulatory procedures are followed. The FDA provides information about the procedures and requirements for expanded access on a [website](#), including a link to FDA's [contact information](#).

### 17.7.1.1 Expanded Access to Investigational Drugs for Individual Patients

Expanded access to investigational drugs may be sought under an “Access Protocol” or an “Access IND”. FDA generally encourages Access Protocols, which are managed and submitted by the sponsor of an existing IND, because it facilitates the review of safety and other information. However, Access INDs for the treatment of individual patients are also available and commonly used when: (1) a sponsor holding an existing IND declines to be the sponsor for the individual patient use (e.g., because they prefer that the physician take on the role of sponsor-investigator); or (2) there is no existing IND.

#### **Sponsor or Manufacturer Approval:**

Prior to submitting to the FDA or IRB, physicians seeking expanded access to an investigational drug should contact the sponsor (e.g., for investigational drugs under a commercial IND) or manufacturer (e.g., for approved drugs under a REMS) to: (1) ensure that the investigational drug can be obtained; (2) determine whether the patient may be treated under an existing IND study, sponsor-held Access Protocol, or if the physician should seek an Access IND; and (3) determine if the drug will be provided free or if there will be a charge. A Letter of Authorization (LOA) from the sponsor or manufacturer should be obtained.

#### **FDA Approval:**

When a commercial sponsor agrees to provide access under an Access Protocol, the sponsor is responsible for managing and obtaining FDA approval and all other sponsor responsibilities. A licensed physician under whose immediate direction an investigational drug is administered or dispensed for expanded access is considered an “investigator” under FDA regulations and is responsible for all investigator responsibilities under [21 CFR 312](#), to the extent they are applicable to expanded access.

If the sponsor or manufacturer declines treatment of the patient under an existing IND study or Access Protocol but agrees to make the investigational drug available for the patient, physicians may apply to the FDA for an individual patient Access IND using Form FDA 3926, a streamlined IND application specifically designed for such requests. Form FDA 3926, and [related guidance](#), is available on a FDA [website](#). Form FDA 3926 includes a section where an investigator can request approval from the FDA for alternative IRB review procedures; these alternative procedures enable review by the IRB Chair (or a Chair-designated IRB member) in lieu of review by the convened IRB. This alternative review procedure is referred to as a “concurrence review” in FDA guidance; however, the IRB Chair must review the same materials and make the same determinations as the convened board would. IRB Chair review can also be used for any post-approval reviews (e.g., unanticipated problems, continuing review, closure, etc.).

When there is an emergency situation and insufficient time to submit a written application to the FDA prior to treatment, a request to FDA for emergency use may be made by telephone (or other rapid means). A written expanded access application must be submitted within 15 days of the FDA’s authorization. For more information on emergency use, see Section 17.7.1.2.

A physician who obtains an Access IND is considered a “sponsor-investigator” and is responsible for the responsibilities of both sponsors and investigators under [21 CFR 312](#), as applicable,

including IND safety reports, annual reports, and maintenance of adequate drug accountability records.

### **IRB Review:**

Unless the conditions that permit an emergency use exemption (see Section 17.7.1.2) are satisfied, IRB approval must be obtained prior to initiating treatment with the investigational drug. When the FDA has authorized the use of alternative IRB review procedures (which can be presumed when the request is made on Form FDA 3926 unless the FDA specifically states that the request is denied), the review may be conducted by the IRB Chair (or designee). Otherwise, the review must be conducted by the convened IRB.

Physicians using investigational drugs under compassionate use should develop and submit an appropriate plan and schedule for treating and monitoring the patient, taking into consideration the nature of the drug and the needs of the patient. The plan should include monitoring to detect any possible problems arising from the use of the drug.

To request IRB approval for single patient expanded access, investigators should contact the IRB office and submit the following in IRBNet:

1. A completed application and any additional documentation noted within it;
2. A copy of the LOA from the Commercial Sponsor or Manufacturer or other documentation supporting sponsor/manufacturer approval;
3. A copy of the information submitted to the FDA (and FDA approval, if available);
4. A copy of the Investigator's Brochure or similar documentation that provides information regarding the potential risks and benefits of the investigational drug;
5. A copy of the plan for treating and monitoring the patient; and
6. A copy of the draft informed consent document.

The IRB may review the expanded access application prior to FDA approval being received but cannot finalize approval until documentation of FDA approval is provided. The IRB will provide the investigator with written documentation of its review.

MaineHealth will consider reliance upon an external IRB for expanded access when the IND is held by a commercial sponsor and an external IRB has approved the protocol and is willing to accept review and oversight of additional investigators/sites. Investigators should contact ORC, to discuss IRB reliance for expanded access protocols.

### **Post-Approval Requirements**

Investigators are responsible for complying with any sponsor or FDA reporting requirements. The post-approval requirements for research described throughout this manual apply, including, but not limited to, prospective IRB approval of any proposed modifications to the plan or materials approved by the IRB unless the change is necessary to eliminate apparent immediate hazard to the subject (in which case it must be promptly reported), reporting of unanticipated problems, noncompliance, complaints, and other reportable information, and for continuing review and study closure, as applicable. **Additionally**, copies of any [follow-up](#)

[submissions](#) to the FDA related to the expanded access use must be submitted to the IRB within 7 business days of the date of submission to the FDA.

### **17.7.1.2 Emergency Use of Investigational Drugs**

FDA regulations permit the use of an investigational drug without IRB approval when an appropriately trained and licensed health care provider determines that IRB approval for the use of the drug cannot be obtained in time to prevent serious harm or death to a patient. The provider is expected to assess the potential for benefit from the use of the drug and to have substantial reason to believe that benefits will exist. The criteria and requirements for this Emergency Use Exemption are explained in Section 17.7.1.3 below.

Approval from the FDA and the Sponsor/Manufacturer must be obtained prior to initiating treatment with the drug.

Providers invoking the emergency use exemption must comply with any applicable FDA follow-up requirements including submission of safety reports, amendments, a summary following completion of treatment, and annual reports.

A copy of reports or amendments submitted to the FDA and any related correspondence must be submitted to the ORC.

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.

### **17.7.1.3 Emergency Use Exemption from Prospective IRB Approval**

Under FDA regulations at [21 CFR 56.104\(c\)](#), FDA exempts the [emergency use of an investigational drug](#) (or biologic classified as a drug) from the requirement for prospective IRB approval, provided that the conditions described below are satisfied and that the emergency use is reported to the IRB within 5 working days. Any subsequent use of the investigational drug in the facility requires IRB approval. 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. If it appears likely that the investigational drug may need to be used again, the IRB may request that a study application is submitted which would cover future uses.

**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.

- **Life-threatening** means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.
- **Severely debilitating** means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

Unless the provisions for an emergency exception from the informed consent requirement are satisfied (see Section 17.7.1.4), 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** after an emergency exemption is used. The IRB Chair or designated IRB member will review the report to verify that circumstances of the emergency use conformed to FDA regulations. This must not be construed as IRB approval, 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 prior to the emergency use, the IRB Chair or designee will review the proposed use, and, if appropriate, 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\(c\)](#). Reports of emergency uses will be brought to the convened IRB for their information. The IRB should review:

1. Justification that the emergency criteria were met
2. Independent physician concurrence
3. Patient status report
4. A copy of the signed consent document, de-identified
5. MaineHealth Application Wizard

Investigators are reminded that they must comply with all other organizational policies and requirements applicable to the use of the investigational or unapproved drugs.

#### **17.7.1.4 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 drug without informed consent when the investigator and an independent physician who is not otherwise participating in the clinical investigation (the emergency use) certify in writing all four of the following conditions:

1. The subject is confronted by a life-threatening situation necessitating the use of the test article;

2. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject;
3. Time is not sufficient to obtain consent from the subject's LAR; and
4. 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 consent exception is invoked. The IRB Chair or designated IRB member will review the report to verify that circumstances of the emergency exception conformed to FDA regulations. The following items should be made available for the IRB Chair or designee's review:

1. Justification that the emergency criteria were met
2. Independent physician concurrence
3. Patient status report
4. MaineHealth Application Wizard

#### **17.7.2 Expanded Access to Investigational and Unapproved/Uncleared 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 are circumstances under which a health care provider may use an unapproved device outside of a clinical study when it is not possible to enroll a patient in a clinical study and the 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
- Compassionate Use (or Single Patient/Small Group Access)
- Treatment Use

Investigators 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 ORC, to ensure that proper regulatory procedures are followed.

FDA has made information about expanded access to medical devices available on a [website](#).

### 17.7.2.1 Compassionate Use of Investigational/Unapproved Medical Devices

The compassionate use provision under expanded access provides a mechanism for accessing investigational devices for an individual patient or small groups of patients when the treating physician believes the device may provide a diagnostic or treatment benefit. Compassionate use can be used for devices being studied in a clinical trial under an IDE for patients who do not qualify for inclusion in the trial, and for devices for which an IDE does not exist. The following criteria must be satisfied:

1. The patient has a life-threatening or serious disease or condition; and
2. No generally acceptable alternative treatment for the condition exists.

The medical device company must agree to make the medical device available for the proposed compassionate use. FDA and IRB approval are required before the device may be used under the compassionate use provision.

#### **FDA Approval:**

When **there is an IDE** for the device, the IDE sponsor submits an IDE supplement requesting approval for the compassionate use under [21 CFR 812.35\(a\)](#).

When **there is not an IDE** for the device, the physician or manufacturer submits the following information to the FDA:

1. A description of the device (provided by the manufacturer);
2. Authorization from the device manufacturer for the use;
3. A description of the patient's condition and the circumstances necessitating treatment or diagnostics (when seeking small group access, the number of patients to be treated);
4. A discussion of why alternative therapies/diagnostics are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition; and
5. The patient protection measures that will be followed, including:
  - a. A draft of the informed consent document that will be used;
  - b. Clearance from the institution as specified by their policies (see below);
  - c. Concurrence (approval) of the IRB Chair or Chair-designated IRB member (prior to FDA request when possible); and
  - d. An independent assessment from an uninvolved physician.

When IRB Chair approval cannot be obtained in advance of the submission to the FDA, the request should indicate that approval from the IRB Chair will be obtained prior to use of the device. Proof of IRB Chair approval must be submitted with the follow-up report to the FDA after the patient is treated (or the diagnostic is used).

When the compassionate use is conducted under an IDE, a licensed provider who receives an investigational device is an "investigator" under FDA regulations and is responsible and

accountable for all applicable investigator responsibilities under [21 CFR 812](#) (IDE regulations), [21 CFR 50](#) (Informed Consent), and [21 CFR 56](#) (IRB).

When the provider obtains an IDE for compassionate use, the provider is considered a “sponsor-investigator” and is responsible for the responsibilities of both sponsors and investigators under [21 CFR 812](#), as applicable, including medical device reports and progress reports .

The provider is also responsible for following all applicable institutional and departmental policies and procedures as it relates to the compassionate use request.

### **IRB Review:**

Unless the conditions that permit an emergency use exemption are satisfied (see Section 17.7.2.3), IRB approval must be obtained prior to initiating treatment with the investigational device. When the request is for single-patient compassionate use, the review may be conducted by the IRB Chair (or designee). Otherwise, the review must be conducted by the convened IRB.

Physicians using medical devices under compassionate use should develop and submit an appropriate plan and schedule for treating and monitoring the patient, taking into consideration the nature of the device and the needs of the patient. The plan should include monitoring to detect any possible problems arising from the use of the device.

To request IRB approval for compassionate use, investigators should contact the IRB office and submit the following via IRBNet:

1. A completed application and any additional documentation noted within it;
2. A copy of the information submitted to the FDA (and FDA approval, if available);
3. A copy of the device brochure, Instructions for Use, or other similar documentation that provides information regarding the potential risks and benefits of the device;
4. A copy of the plan for treating and monitoring the patient; and
5. A copy of the draft informed consent document.

The IRB may review the expanded access application prior to FDA approval being received but may condition approval upon receipt of FDA approval. The IRB will provide the investigator with written documentation of its review.

MaineHealth will consider reliance upon an external IRB for Compassionate Use protocols on a case-by-case basis when the IDE is held by a commercial sponsor and an external IRB has already approved the protocol and is willing to accept review and oversight of additional investigators/sites. Investigators should contact the ORC, to discuss IRB reliance for Compassionate Use protocols.

### **Post-Approval Requirements**

Investigators are responsible for complying with any sponsor or FDA reporting requirements. The post-approval requirements for research described throughout this manual apply, including, but not limited to, prospective IRB approval of any proposed modifications to the plan or materials approved by the IRB unless the change is necessary to eliminate apparent immediate hazard to the subject (in which case it must be promptly reported), reporting of unanticipated problems, noncompliance, complaints, and other reportable information, and for continuing review and study closure, as applicable. **Additionally**, a follow-up report to the FDA is required following a compassionate use by whomever submitted the original request to the FDA. The report should include summary information regarding patient outcome and any problems that occurred as a result of the device. A copy of the follow-up report to the FDA and any other post-approval submissions or reports to the FDA must be submitted to the IRB within 7 business days of the date of submission to the FDA.

### **17.7.2.2 Treatment Use of Investigational/Unapproved Medical Devices**

During the course of a clinical trial under an IDE, if the data suggest that the device under study is effective, the trial may be expanded to include additional patients with life-threatening or serious diseases under the Treatment Use provision for expanded access. “Treatment Use” also applies to the use of a device for diagnostic purposes under these same conditions. [[21 CFR 812.36](#)]

The following criteria must be satisfied for Treatment Use to apply:

1. The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition;
2. There is no comparable or satisfactory alternative device available to treat or diagnose the disease or condition in the intended patient population;
3. The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or all clinical trials have been completed; and
4. The sponsor of the controlled clinical trial is pursuing marketing approval/clearance of the investigational device with due diligence.

The IDE sponsor is responsible for applying for a Treatment Use IDE.

A licensed provider who receives an investigational device for treatment use under a Treatment Use IDE is an “investigator” under FDA regulations and is responsible and accountable for all applicable investigator responsibilities under [21 CFR 812](#) (IDE regulations), [21 CFR 50](#) (Informed Consent), and [21 CFR 56](#) (IRB).

#### **IRB Review:**

IRB approval is required before the investigational device/diagnostic is used. Standard procedures for IRB submissions, and organizational approvals are to be followed.

MaineHealth will consider reliance upon an external IRB for Treatment Use IDE protocols on a case-by-case basis when an external IRB has already approved the protocol and is willing to

accept review and oversight of additional investigators/sites. Investigators should contact the ORC to discuss IRB reliance for Treatment Use IDEs.

### **Post-Approval Requirements**

Investigators are responsible for complying with any sponsor or FDA reporting requirements. The post-approval requirements for research described throughout this manual apply, including, but not limited to, prospective IRB approval of any proposed modifications to the plan or materials approved by the IRB unless the change is necessary to eliminate apparent immediate hazard to the subject (in which case it must be promptly reported), for reporting of unanticipated problems, noncompliance, complaints, and other reportable information, and for continuing review and study closure, as applicable. **Additionally**, the semi-annual (applicable until the marketing application is filed) or annual (applicable after the marketing application is filed) progress report from the sponsor must be submitted to the IRB within 7 business days of receipt.

#### **17.7.2.3 Emergency Use of Investigational Devices**

FDA regulations permit the [emergency use of an investigational or unapproved device](#) without prior approval by the FDA or IRB when an appropriately trained and licensed health care provider determines that:

- The patient has a life-threatening or serious disease or condition that needs immediate treatment;
- No generally acceptable alternative treatment for the condition exists; and
- Because of the immediate need to use the device, there is no time to use existing procedures to obtain FDA approval for the use.

FDA expects the provider to make the determination that the above criteria are satisfied, to assess the potential for benefit from the use of the unapproved device, and to have substantial reason to believe that benefits will exist. **Because prior FDA approval is not required, FDA expects providers planning the emergency use of an investigational device to obtain as many of the following as possible:**

- An independent assessment from an uninvolved physician;
- Authorization from the device manufacturer;
- Concurrence of the IRB Chair or designee;
- Institutional clearance; and
- Informed consent from the patient or legally authorized representative.

At MaineHealth, providers planning the emergency use of an investigational or unapproved device must contact the HRPP/IRB office as early in the process as possible. The following are required to be submitted, along with satisfaction of FDA requirements above:

1. Justification that the emergency criteria were met

2. Independent physician concurrence
3. Patient status report
4. MaineHealth Application Wizard

The IRB Chair or designee will review the information provided and determine whether the use conforms with FDA's requirements and expectations and whether the provisions for the protection of the patient appear adequate using the applicable criteria at 21 CFR 50 and 56 as guidelines (e.g., minimization of risks, risk/benefit, safety monitoring, informed consent, etc.).

The emergency use must be reported to the FDA by the IDE Sponsor, when one exists, or by the provider if no IDE exists. Information regarding what to include in the report and where to submit it is available on [FDA's website](#). When the provider is responsible for the FDA report, a copy of the report and any related correspondence must be submitted to the ORC.

Reports of emergency uses will be brought to the convened IRB for their information.

Providers are reminded that they must comply with all other organizational policies and requirements applicable to the use of the investigational or unapproved devices.

## **17.8 Charging Subjects for Investigational Products**

FDA regulations do not prohibit charging subjects or their insurers for investigational products so long as those charges comply with specified criteria. FDA approval of such charges does not obviate the investigator's and IRB's responsibility to minimize risks to subjects (Beneficence), to ensure that the risks and burdens associated with research are equitably distributed (Justice), and to ensure that subjects are properly informed and not unduly influenced to accept an otherwise unacceptable risk or cost in order to access a benefit (Respect for Persons). Any costs to subjects or insurers must be described in the IRB application and informed consent document.

### **17.8.1 Charging for Investigational Medical Devices and Radiological Health Products**

IDE regulations allow sponsors to charge for an investigational device, however, the charge may not exceed the amount necessary to recover the costs of manufacture, research, development, and handling of the investigational device [[21 CFR 812.7\(b\)](#)]. Sponsors must justify the proposed charges for the device in the IDE application, state the amount to be charged, and explain why the charge does not constitute commercialization [[21 CFR 812.20\(b\)\(8\)](#)].

### **17.8.2 Charging for Investigational Drugs and Biologics**

In 2009, FDA updated its rules at 21 CFR 312 regarding charging for Investigational Drugs Under an IDE. These rules:

- 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 for an expanded access for treatment use [[21 CFR 312.8\(c\)](#)]
- Establish criteria for determining what costs can be recovered when charging for an investigational drug [[21 CFR 312.8\(d\)](#)]

Additional information is available in FDA guidance: [Charging for Investigational Drugs Under an IND — Questions and Answers](#).



## 18 Unanticipated Problems Involving Risks to Subjects or Others: A type of Reportable New Information

Regulations require an organization to have written procedures for ensuring prompt reporting of “unanticipated problems involving risk to subjects or others” (UPs). At MaineHealth, these are a type of ‘Reportable New Information’ (RNI).

This section provides definitions and procedures for the reporting of UPs to the MaineHealth IRB. Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB as well as the internal reporting requirements outlined in Section 8.3.

In conducting its review of protocol deviations, noncompliance, subject complaints, and other reportable events, the IRB will also consider whether the event or issue was caused by, contributed to, or otherwise related to an UP.

### 18.1 Definitions

**Unanticipated problems involving risk to participants or others.** Unanticipated problems involving risks to subjects or others (UPs) refer to any incident, experience, outcome, or new information that:

1. Is unexpected; **and**
2. Is at least 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

UPs also encompass Unanticipated Adverse Device Effects, as defined below.

**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, whether or not considered related to 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.

**Serious Adverse Event:** An adverse event is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent

or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

**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\(s\)](#)].

## 18.2 Procedures

### 18.2.1 Reporting

Unanticipated Problems are reported to the MaineHealth IRB using the “MaineHealth-Progress Report, Study Completion, Reportable New Information Form’ Wizard in IRBNet.

Adverse events (serious or not) in clinical trials must be reported to the sponsor in compliance with FDA regulations and sponsor requirements. Unless specifically required by the IRB for a given protocol, the MaineHealth IRB does not accept reports of adverse events that are not UPs.

**Serious Adverse Events** that (a) meet the definition of a UP, i.e., related to the study and unanticipated, and (b) either occurs at MaineHealth, or occurred at another site resulting in study-wide change to the protocol or informed consent form must be reported **within 5 business days** using the form referenced above.

**If the Serious Adverse Event is, or results in, death**, and (a) meets the definition of a UP, i.e., related to the study and unanticipated, and (b) either occurred at MaineHealth, or occurred at another site resulting in study-wide change to the protocol or informed consent form, then it must be reported **within 48 hours** using the form referenced above.

Investigators must report UPs to the IRB within **10 business days** of occurrence (or notification, if from outside of MaineHealth) using the form referenced above. If investigators are uncertain but believe that the event might represent an UP, a report should be submitted.

The following are examples of UPs:

1. A breach of confidentiality or loss of research data (e.g., a laptop or thumb drive is lost or stolen);

2. 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);
3. Incarceration of a research subject after enrollment on an active research study (requiring additional regulatory review to ascertain added risk to the subject as a result of incarceration)
4. 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);
5. 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 groups reveals higher rate in the drug treatment arm versus a control). A summary and analyses supporting the determination should accompany the report;
6. 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;
7. 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;
8. AEs involving direct harm to subjects enrolled by the local investigator which in the opinion of the investigator or sponsor, may represent an UP;
9. IND Safety Reports from sponsors that meet the criteria for an UP. Such reports must be accompanied by an analysis from the sponsor explaining why the report represents an UAP and whether it has been reported to the FDA as such;
10. Unanticipated adverse device effects (UADEs);
11. Any other AE 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.

12. Reports (including reports from DSMBs/DMCs) that indicate that risks are greater than previously known or that indicate that the research should be modified, suspended, or halted.
13. Sponsor or lead investigator/coordinating center-imposed suspension or termination of some or all research activities;
14. An unanticipated event related to the research that exposes subjects to potential risk but that does not involve direct harm to subjects;
15. An unanticipated event related to the research that results in actual harm or exposes individuals other than the research subjects (e.g., investigators, research assistants, students, the public, etc.) to potential risk;
16. New information that indicates increased risk, new risk(s), or decrease to potential benefit from what was previously understood. Examples include:
  - a. An interim analysis or safety monitoring report indicates that the frequency or magnitude of harms or benefits may be different than initially presented to the IRB;
  - b. A report or publication that indicates the risks, benefits, or merit of the research are different from what was previously understood.

#### **18.2.2 Review Procedures**

1. Upon receipt of the MaineHealth-Progress Report, Study Completion, Reportable New Information Form, the IRB staff pre-reviews the submission and, if needed, contacts the investigator for corrections or additional information.
2. The IRB Chair or designated reviewer receives and reviews the report and makes an initial determination as to whether the event represents an UP. If needed, the Chair or designee may request additional information from the investigator, sponsor, or others (including study committees, such as data monitoring committees, data safety monitoring boards, or steering committees).
3. If the reviewer determines that the problem does not meet the definition of an UAP, they will determine whether any additional actions are necessary to ensure the protection of human subjects. As warranted, the reviewer may refer the matter to the convened IRB for review. The results of the review will be recorded in IRBNet and communicated to the investigator.
4. If the reviewer determines that the event may be an UAP, the report will be referred for review by the convened IRB. The convened IRB will determine whether the event is a UAP and whether any additional actions, such as those outlined below, are necessary to ensure the protection of human subjects. If needed, the IRB may request additional information from the investigator, sponsor, or others (including study committees, such as data monitoring committees, data safety monitoring boards, or steering committees).

The results of the review will be recorded in the IRB minutes and communicated to the investigator.

5. Based upon the circumstances, the IRB may take any of the following actions, or others, to ensure the protection of human subjects:
  - a. Requiring modifications to the protocol or plan or procedures for implantation of the research (Research Plan) as described in the application and other materials submitted to the IRB;
  - 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 rights, welfare, or willingness to continue participation);
  - f. Providing additional information to past participants;
  - g. Requiring additional training of the investigator and/or study staff;
  - h. Requiring that current subjects re-consent to participation;
  - i. Monitoring the research;
  - j. Monitoring consent;
  - k. Reporting or referral to appropriate parties (e.g., the IO, Privacy Officer, Risk Management, etc.);
  - l. Suspending IRB approval;
  - m. Terminating IRB approval;
  - n. Other actions as appropriate given the specific circumstances.

When the IRB determines that an event is an UAP, the IRB staff will follow the procedures for reporting to regulatory agencies, sponsors, and organizational officials in Section 22. When appropriate, a preliminary report may be submitted while more information is obtained to inform the determination or actions.

## 19 Noncompliance

This section provides definitions and procedures for the reporting and review of known or suspected noncompliance for research under the oversight of the MaineHealth IRB. Research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in Section 8.3.

In conducting its review of protocol deviations, unanticipated problems, subject complaints, and other reportable events, the IRB will also consider whether the event or issue was caused by, contributed to, or otherwise related to noncompliance.

### 19.1 Definitions

**Noncompliance** is defined as the failure to follow federal, state, or local regulations governing human subject research, institutional policies related to human subject research, or the requirements or determinations of the IRB. Noncompliance may be minor or sporadic or it may be serious or continuing.

**Serious Noncompliance** is defined as noncompliance 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 policies and/or federal regulations may also constitute serious noncompliance.

**Continuing Noncompliance** is defined as a pattern of noncompliance that, in the judgment of the convened IRB, suggests a likelihood that instances of noncompliance will continue unless the IRB or institution intervenes.

**Allegation of Noncompliance.** Allegation of Noncompliance is defined as an unproved assertion of noncompliance.

### 19.2 Reporting

Investigators and their study staff are required to report instances of possible noncompliance to the IRB within **7 working days** of discovery using the MaineHealth – Progress Report/Study Completion/Reportable New Information wizard in IRBNet. Additionally, anyone may report concerns of possible noncompliance to the HRPP or IRB verbally, by email, or other means. In such cases, the reporting party is responsible for making these reports in good faith, maintaining confidentiality and, unless reporting anonymously, cooperating with any subsequent fact-finding in relation to the report.

If an individual, whether investigator, study staff or other, is uncertain whether there is cause to report noncompliance, he or she may contact the ORC Director, IRB Manager, or Chair directly to discuss the situation informally.

### 19.3 Review Procedures

1. Upon receipt of the submission package, the IRB staff pre-reviews the submission and, if needed, contacts the investigator for corrections or additional information. If the report

came from someone other than the investigator or study team verbally, by email, or by other means, the ORC Director, IRB Manager, or assigned staff will develop a written report summarizing the available information and will upload the report into the IRB electronic system. If the information provided suggests that subjects may be at risk of harm without immediate intervention, the ORC Director, IRB Chair, and, when appropriate, the IO, will be notified so that they can take any necessary steps to ensure the safety of subjects and investigate the matter, and contact appropriate institutional officials responsible in accordance with other applicable MaineHealth policies (e.g., research misconduct).

2. The IRB Chair or designated reviewer receives and reviews the report and makes an initial determination as to whether the event represents noncompliance, and, if so, whether the noncompliance may be serious or continuing. If needed, the reviewer may request additional information from the investigator or others. When circumstances warrant, the ORC Director or IRB Manager may bypass this step and assign the report for convened board review.
3. If the reviewer determines that the event or issue is not noncompliance, or is noncompliance but not serious or continuing, they will review any proposed corrective and preventative action plans and determine if the plan is acceptable as proposed or if modifications to the plan or additional actions are required. As warranted, the reviewer may refer the matter to the convened IRB for review. The results of the review will be recorded in the electronic system and communicated to the investigator.
4. If the reviewer determines that the event or issue may be serious or continuing noncompliance, the report will be referred for review by the convened IRB. The convened IRB will determine whether the event is serious or continuing noncompliance. The IRB will review any proposed corrective and preventative action plans and determine if the plan is acceptable as proposed or if modifications to the plan or additional actions, such as those outline below, are necessary to ensure the protection of human subjects. If needed, the IRB may request additional information from the investigator or others. The results of the review will be recorded in the IRB minutes and communicated to the investigator.
5. When the IRB determines that an event is serious or continuing noncompliance, the IRB may take any of the following actions, or others, to ensure the protection of human subjects:
  - a. Requiring modifications to the protocol or 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. Requiring that current subjects re-consent to participation
  - i. Monitoring the research
  - j. Monitoring consent
  - k. Reporting or referral to appropriate parties (e.g., the IO, Compliance, Risk Management, Privacy)
  - l. Suspending IRB approval
  - m. Terminating IRB approval
  - n. Other actions as appropriate given the specific circumstances
6. When the IRB determines that an event is serious or continuing noncompliance, the IRB staff will follow the procedures for reporting to regulatory agencies, sponsors, and organizational officials in Section 22. When appropriate, a preliminary report may be submitted while more information is obtained to inform the determination or actions.
  7. Investigators may request that the IRB reconsider its determination by following the procedures in Section 11.4.

## **20 Complaints**

The HRPP & IRB will be responsive and sensitive to the complaints or concerns expressed by subjects or others and will respond to all complaints or concerns in a confidential and timely manner. The PI and all other research team members are responsible for the safety and welfare of all subjects enrolled in their studies. When investigators or team members hear complaints or concerns from subjects, he or she will try to resolve them.

Investigators conducting research under the auspices of MaineHealth must report complaints (that cannot be resolved by the study team) to the MaineHealth HRPP regardless of who serves as the IRB of record. Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in Section 8.3. Investigators conducting research under the oversight of the MaineHealth IRB report complaints using the MaineHealth – Progress Report/Study Completion/Reportable New Information wizard in IRBNet within 10 business days of receiving the complaint. Investigators are encouraged to contact the IRB Manager or ORC Director when they are having difficulty resolving a complaint or concern, and whenever circumstances warrant (e.g., immediate attention is needed).

When the HRPP or IRB office is the direct recipient of complaints or concerns, the staff will do the following:

1. Document the complaint or allegation. When appropriate, the staff may request that the subject submit the complaint in writing.

2. Reassure the subject that the HRPP/IRB will take all necessary measures to inquire into the circumstances and to address the issue.
3. Provide written confirmation of receipt of the complaint to the subject, if the subject is willing to provide contact information.
4. Convey the information to the IRB of record in a timely manner.
5. When appropriate, contact the investigator for additional information or to assist with resolution.
6. When appropriate, contact other resources (e.g., Risk Management, Patient Relations, Privacy Officer) to assist with information-gathering or resolution.

For research under the oversight of the internal IRB, the IRB Chair or designee will consider the complaint or concern and take any reasonable steps necessary to investigate and/or resolve the issue, if appropriate, prior to review and consideration by the IRB. A report will be provided to the IRB at the next available meeting if the research is subject to convened IRB review, or provided to the designated expedited reviewer if the research is eligible for expedited review. When reviewing complaints, the IRB will consider whether the complaint was the result of, or related to, an UAP or noncompliance, and, if so, will follow the relevant procedures. The IRB Chair or designated expedited reviewer may refer any complaint for review by the convened IRB. The IRB minutes, or reviewer comments for expedited reviews, will reflect the action(s) taken and, if necessary, notice to the appropriate officials and/or agencies.

The HRPP will maintain a record of complaints and concerns and will document the investigation and resolution. The complainant will be notified promptly following resolution of the complaint or concern, when appropriate, and if contact information has been provided. If the HRPP or IRB receives a complaint, or identifies information while investigating a complaint, that is indicative of possible misconduct in research, appropriate institutional officials will be notified immediately in accordance with MaineHealth policy.

## 21 Other Reportable Information

When research is under the oversight of the MaineHealth IRB, in addition to UAPs, noncompliance, and complaints, any change to the research implemented without IRB approval and any information that may impact the rights, safety, or welfare of subjects or inform the IRB's oversight of the research must be reported to the IRB within **7 working days** of discovery using the MaineHealth – Progress Report/Study Completion/Reportable New Information wizard in IRBNet. Investigators conducting research under the oversight of an external IRB must comply with the reporting requirements of the external IRB and the internal reporting requirements outlined in Section 8.3.

Other reportable information includes, but is not limited to, the following:

1. Changes made to the research without prior IRB approval to eliminate apparent immediate hazards to the subject(s);
2. Protocol Deviations - any variation from the IRB approved research plan that happens without prior review and approval of the IRB and isn't necessary to eliminate apparent immediate hazards to the subject(s);
3. Monitoring, audit, and inspection reports in accordance with Section 2.1 of this manual;
4. Notice of:
  - a. Any negative actions by a government oversight office, including, but not limited to, OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated (classification as "OAI" is typically made after FDA has had the opportunity to review the responses to a 483), FDA Restrictions Placed on IRBs or Investigators, and any corresponding compliance actions taken under non-US authorities related to human research protections.
  - b. Any litigation, arbitration, or settlements initiated related to human research protections.
  - c. Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding human subjects research conducted at or by [INSERT ORGANIZATION] or [INSERT ORGANIZATION]'s program for the protection of human research participants.

NOTE: The above events (4.a, b, and/or c) must be reported to the HRPP/IRB office by phone or email **as soon as anyone becomes aware**, with the formal submission within the 7-day timeline as noted above. See Section 22 for more information.

5. Sponsor or coordinating center reports;
6. Data Safety Monitoring reports, including reports from DSMBs, DMCs, and others;
7. Enrollment or inclusion of vulnerable populations not previously approved by the IRB for the study (e.g., prisoner, pregnant woman, neonate, child, adult with impaired decision-making capacity);

8. When an existing subject becomes a member of a vulnerable population not previously approved by the IRB for inclusion in the study (e.g., incarceration, pregnancy, or change in decision-making capacity of an already enrolled subject);
9. Holds, suspensions, or terminations of a study, in part or in full, by an investigator, sponsor, or others;
10. Changes that impact the ability of the PI to conduct or supervise the study, temporarily or permanently;
11. Changes that impact the qualifications of investigators or research staff members such as actions taken by regulatory authorities, licensing boards, or credentialing committees;
12. New information that may impact the rights, welfare, or willingness of subjects to continue in the research.

### **21.1 Review Procedures**

1. Upon receipt of the report, the IRB staff pre-reviews the submission and, if needed, contacts the investigator for corrections or additional information. If the information provided suggests that subjects may be at risk of harm without immediate intervention, the ORC Director, IRB Chair, and, when appropriate, the IO, will be notified so that they can take any necessary steps to ensure the safety of subjects, investigate the matter, and where applicable, forward the matter to appropriate institutional officials in accordance with MaineHealth policy (e.g., research misconduct, etc.).
2. The IRB Chair or designated reviewer receives and reviews the report and if the report may represent an UAP or noncompliance, reviews the report as described in Section 18 or 19. When circumstances warrant, the ORC Director or IRB Manager may bypass this step and assign the report for convened board review.
3. If the reviewer determines that the event or issue is not noncompliance or an UAP, they will review the event or issue, any proposed corrective and preventative action plans, and determine if any additional actions are needed to ensure the protection of human subjects. As warranted, the reviewer may refer the matter to the convened IRB for review. The results of the review will be recorded in IRBNet and communicated to the investigator.

## **22 Reporting to Federal Agencies, Departments, and Organizational Officials**

Federal regulations require prompt reporting to appropriate institutional officials and, as applicable, the federal department or agency (e.g., OHRP, FDA), of (i) any unanticipated problems involving risks to subjects or others; (ii) any serious or continuing noncompliance with the applicable federal regulations or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval. MaineHealth IRB complies with this requirement as follows. When research is under the oversight of an external IRB, the terms of the agreement with that IRB will guide reporting.

### **22.1 Procedures**

ORC staff will initiate these procedures as soon as the IRB takes any of the following actions:

1. Determines that an event may be considered an unanticipated problem involving risks to participants or others
2. Determines that noncompliance was serious or continuing
3. Suspends or terminates approval of research

The ORC Director or designee is responsible for preparing reports or letters which includes the following information (as applicable):

1. Reason for the report (Unanticipated problem involving risks to subjects or others, serious or continuing noncompliance, suspension or termination of IRB approval)
2. Name of the involved institution(s)
3. Title of the research project and/or grant proposal in which the problem occurred
4. Name of the investigator on the project
5. Number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement)
6. A detailed description of the problem including the findings of the organization and the reasons for the IRB's decision
7. Actions the institution is taking or plans to take to address the problem (e.g., revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring, etc.)
8. Plans, if any, to send a follow-up or final report by the earlier of
  - a. A specific date
  - b. When an investigation has been completed or a corrective action plan has been implemented
9. The IRB Chair and the IO review the letter and recommend modifications as needed

10. The IO is the signatory

11. The ORC Director or designee sends a copy of the report to:

- The IRB Chair
- The IO
- Federal agencies, as follows:
  - a. OHRP, if the study is subject to DHHS regulations or subject to a DHHS FWA.
  - b. If the study is conducted or supported by a Common Rule agency other than DHHS, the report is sent to OHRP or the head of the federal agency, as required by the agency.
  - c. If the study is conducted or supported by a federal agency that has not adopted the Common Rule, and reporting is required, the report is sent to the party identified by the agency.
  - d. FDA, if the study is subject to FDA regulations.

Note: 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 another party (e.g., sponsor).

- Sponsor, if the study is sponsored
- Investigator, if not previously notified of the reporting requirement.
- Others (either internal or external) as deemed appropriate by the ORC Director and IO
- AAHRPP, as required in Section 22.2

The ORC Director ensures that all steps of this policy are completed within 30 working days of the determination. For more serious actions, the Director will expedite reporting. If additional time is needed to gather facts, or determine corrective actions, a preliminary report will be submitted within 30 days, to be followed by a final report as described above.

## **22.2 Reporting to AAHRPP**

MaineHealth's HRPP is accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). In addition to the information that MaineHealth routinely provides to AAHRPP in annual reports and the re-accreditation application, AAHRPP requires that any of the following are reported to AAHRPP asap but generally within 48 hours after the organization or any researcher (if the researcher is notified rather than the organization) becomes aware:

- Any negative actions by a government oversight office, including, but not limited to, OHRP Determination Letters, FDA Warning Letters, FDA 483 Inspection Reports with official action indicated, FDA Restrictions Placed on IRBs or Investigators, and corresponding compliance actions taken under non-US authorities related to human research protections;

- Any litigation, arbitration, or settlements initiated related to human research protections; and/or
- Any press coverage (including but not limited to radio, TV, newspaper, online publications) of a negative nature regarding MaineHealth's HRPP.

The HRPP Director (or designee) is responsible for ensuring that such reports are made to AAHRPP and for informing appropriate organizational officials. Investigators, research staff, HRPP/IRB staff, IRB members, and other organizational officials or offices (e.g., the IO, Compliance, Legal, etc.) are responsible for informing the HRPP/IRB office as soon as they become aware of any of the above so that these reporting obligations may be fulfilled.

## **23 Investigator Responsibilities**

Principal Investigators (PIs) are ultimately responsible for the conduct of research. PIs may delegate tasks to appropriately trained and qualified members of their research team. However, PIs must maintain oversight and retain ultimate responsibility for the proper conduct of the research.

Within the regulations, the term ‘investigator’ refers to individuals involved in the design, conduct, or reporting of the research. Such involvement could include one or more of the following:

- Designing the research
- 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
- Studying, interpreting, or analyzing identifiable private information or data for research purposes.

### **23.1 Responsibilities**

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. Develop a research plan that ensures 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, 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 the confidentiality of data;
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; and
  - g. When appropriate, a plan to ensure the availability of medical, psychological, or other services that subjects might require as a result of their participation.
9. Ensure 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 Maine and the policies of MaineHealth;
  10. Ensure 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. Ensure that all persons assisting with the research are adequately trained and informed about the protocol and research implementation 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 PHI is used, legally effective HIPAA authorization is obtained for each subject unless a 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, any associated grant or contract, and, when applicable, 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 LAR, 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 the research begins;
  20. Ensure that all required reviews and approvals (e.g., Internal Services Reviews, COI, IBC, Radiation Safety Committee, Scientific Review Committee) are in place before initiating 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, noncompliance, suspensions, terminations, and any other reportable events to the IRB and the organization, as required by regulations and policy;
24. Notify the IRB if information becomes available that suggests a change to the potential risks, benefits, merit, or feasibility 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 described to and approved by the IRB and as required by required by regulations, agreements, and policies;

Additional investigator responsibilities, including specific responsibilities for investigators engaged in FDA-regulated research are described throughout this manual.

### **23.1.1 Record Retention**

Investigator research records, including, but not limited to, signed consent forms and HIPAA authorizations, subject records and data, test article records, IRB records (submission materials, IRB determinations and associated documentation, correspondence to and from the IRB, etc.), and sponsor/grant records must be retained in accordance with regulatory, organizational, IRB, sponsor or grantor, and journal or publication standards. 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. When research is sponsored or grant-supported, consult the contract, grant terms, or other relevant agreements prior to destroying or transferring any records. If there are questions or allegations about the validity of the data or the appropriate conduct of the research, all records must be retained until such questions or allegations have been completely resolved.

The following summarizes a few of the more common regulatory requirements:

1. **OHRP** – research records must be retained for at least 3 years after the completion of the research
2. **HIPAA** – Research authorizations, or documentation of waivers or alterations of authorization, must be held for a minimum of 6 years after the authorization or waiver/alterations was last obtained or in effect, whichever is later
3. **FDA – Drugs** (& biologics classified as drugs) - For a period 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 indication, until 2 years after the investigation is discontinued and FDA is notified

4. **FDA – Devices** (& biologics classified as devices) - For a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

### **23.2 Investigator Concerns**

Investigators who have concerns or regarding the conduct of research at MaineHealth, MaineHealth’s HRPP or IRB(s), or the external IRBs MaineHealth relies upon should convey them to the Director of Research Compliance, the IO or other responsible parties (e.g., Department Chair), when appropriate. The recipient of the concern 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 IRB Chair and IRB Manager are available to address investigators’ questions, concerns, and suggestions.

Anyone with concerns may also report via [MaineHealthri\\_info@MaineHealth.org](mailto:MaineHealthri_info@MaineHealth.org).

Consistent with MaineHealth policies, there will be no retaliation against any individuals who report concerns in good faith.

## 24 Sponsored Research

It is MaineHealth policy that any sponsored research conducted under the auspices of the MaineHealth 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.

### 24.1 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.

### 24.2 Responsibility

Sponsor grants, contracts, and other written agreements will be reviewed for the following by Grants and Contracts, 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 to the MaineHealth IRB 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 MaineHealth IRB.
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 MaineHealth will be notified of the results in order to consider informing participants
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.

## **25 Conflict of Interest in Research**

It is MaineHealth 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.

### **25.1 Researcher Conflicts of Interest**

Pursuant to the Policy on Conflict of Interest in Research ("COI Policy"), MaineHealth maintains a Research Conflict of Interest Committee (RCOIC) Committee). MaineHealth IRB collaborates with the RCOIC to ensure that COI of investigators and research team members are identified and managed before the IRB completes its review of any research application.

#### **25.1.1 Procedures**

##### **25.1.1.1 Disclosure of Researcher COI**

In addition to other triggers for reporting disclosures (e.g., time of funding application, annual institutional requirements), investigators must disclose their significant financial interests (SFI- as defined in the COI policy) each time a human subject proposal on which they are named is submitted to the IRB or to a Central IRB for research to be conducted at MaineHealth or under the auspices of MaineHealth. Specific triggering events involving human research are: new study submissions, continuing reviews, additions of a new investigator, and whenever an investigator updates their MaineHealth COI disclosure indicating a new or changed interest.

All research disclosures are made via an electronic financial disclosure form to be maintained by the ORC. The ORC will perform an initial review of submitted disclosures and will determine the presence of an SFI as defined in the COI Policy. Where an SFI is deemed present, and there is possible or probable potential for the SFI to influence the design, conduct and/or reporting of a research study (i.e., an FCOI exists), the Investigator and their Department Chief (or direct supervisor) will be contacted by an RCOIC delegate and asked to provide, for RCOIC review, one or both of the following:

- Documentation, to include specific detail, addressing factors that may contribute to, or negate, a potential finding by the RCOIC of an actual (or perceived) conflict of interest.
- A proposal to include actions or methods to be taken to prevent, or manage, an actual (or perceived) conflict of interest.

The case with all supporting documents will be reviewed a convened meeting of the RCOIC. If an FCOI is found, a conflict management plan (CMP) is drafted and submitted to the IRB for further review and consideration. When the research is under an external IRB, any conflicts identified as the result of COI review and any CMP are provided to the external IRB in accordance with the IRB reliance agreement.

#### **25.1.1.2 Evaluation of COI**

The IRB will review COIs and CMPs to determine:

1. Whether the COI affects the rights or welfare of research subjects;
2. Whether the COI might adversely affect the integrity or credibility of the research or the research program; and
3. Whether the CMP effectively protects research subjects and the integrity and credibility of the research and the research program.

In evaluating COIs and CMPs, among other factors the IRB will consider:

1. How the research is supported or financed;
2. The nature and extent of the conflict;
3. The role and responsibilities of the conflicted individual in the design, conduct, and reporting of the research; and
4. The ability of the conflicted individual to influence the outcome of the research.

#### **25.1.1.3 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 RCOIC, the IRB may include additional requirements and may also make modification requests. 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 RCOIC.

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; and/or
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. A research project will not be approved unless and until the CMP has been approved by the IO, the RCOIC, and the IRB.

## **25.2 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 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 himself or herself from the deliberations and vote by leaving the room.

All members and alternate members of the IRB complete a conflict disclosure when first appointed and annually thereafter or sooner when their circumstances change. These forms are submitted to the Office of Research Compliance. Disclosures of COI are reviewed by the IRB Chair who will work with the member to eliminate or manage the disclosed COI. 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., studies from X sponsor; studies using X device/drug; studies involving X investigator). The RRC 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 reminds members of conflicts at convened meetings as needed to ensure recusal. IRB staff may consult with the IRB Chair 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 COI Policy for a definition of significant financial interests) related to the research being reviewed; or
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 remind IRB members at the beginning of each convened meeting that if any members have a COI regarding any of the items to be reviewed, 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.

If an IRB member is conflicted on an agenda item for review by the convened board, the conflicted member will not have access to the committee review in IRBNet.

IRB members with a conflicting interest are excluded from being counted towards quorum. Recusals of members with COIs are recorded in the minutes.

## **25.3 Institutional Conflict of Interest**

As an organization that conducts and reviews research involving human subjects, MaineHealth recognizes its obligation to protect the rights and welfare of those subjects, and ensure the integrity of the research and the human research protection program. Toward this end, the financial interests of MaineHealth or its senior administrative officials must be identified, evaluated, managed, and minimized or eliminated in order to ensure that meeting that obligation is not jeopardized.

### **25.3.1 Definition of Institutional Financial Conflicts of Interest**

An “Institutional Financial Conflict of Interest” arises in human subjects’ research when a financial interest of MaineHealth may affect or appear to affect the design, conduct, reporting, review, or oversight of the human subjects’ research. Institutional financial conflicts of interest are of significant concern when they create the potential for inappropriate influence over a human subjects’ research project, particularly to the integrity of the research and the safety and care of subjects enrolled in the research. All forms of potential Institutional Financial Conflicts of Interest in human subjects’ research require disclosure, evaluation, and either management or elimination under this Policy.

Note that it is MaineHealth’s policy to prohibit receipt of gifts or gifts in kind from a potential commercial sponsor of human subjects research or a company that owns or controls products being studied or tested in human subjects research.

An “Institutional Financial Conflict of Interest” (IFCOI) exists when:

1. MaineHealth receives or might reasonably be expected to receive royalty income from the sale of a product covered by any patent, license or copyright, whether issued or pending, held by, and is proposed to be used in human subjects’ research projects, at MaineHealth;
2. MaineHealth holds or proposes to hold, directly or indirectly, any equity interests of any amount (or entitlement to the same), in research sponsors of human subjects’ research projects, whether such research sponsor is public or non-public, through its technology licensing activities or investments related to such activities;

and/or

3. MaineHealth Senior Administrative Officials with direct responsibility for human subject research (or their spouse, dependent children), as defined in Section II below:
  - a. Hold positions such as an officer, trustee, director, employee or consultant in commercial research sponsors, or any company that owns or controls products being studied or tested in human subjects
  - b. Receive remuneration from commercial research sponsors, or any company that owns or controls products being studied or tested in human subjects. Remuneration includes salary and any payment for services not otherwise identified as salary (e.g., consulting fees, honoraria, paid authorship);

c. Hold any equity interest (e.g., stock, stock option, or other ownership interest) in commercial research sponsors, or any company that owns or controls products being studied or tested in human subjects

d. Hold Intellectual property rights and interests (e.g., patents, copyrights), royalties from such rights, etc. relating to products being studied or tested in human subjects

### **25.3.2 Reporting**

The ORC, in consultation with the RCOIC, will be advised of any annual disclosures from individuals in which significant financial interests relating to human research are identified. The ORC will, in turn, contact the affected individuals to receive confirmation that they will not be involved in the scientific merit, resource review, or any other review relating to research with which they have an SFI. Such confirmation will constitute the management plan that mitigates the potential COI (see also 'Conflict Management Plan' section below).

### **25.3.3 Review and Evaluation**

IRB proposals submitted in IRBNet will be assessed (in advance of IRB review and approval) by an RRC for potential IFCOI by assessing applicability of information contained within the reports referred to above. As a matter of policy, MaineHealth will not participate in a human subjects' research project when it has an IFCOI. An exception to this policy may be made only when the Institutional Review Board, in consultation as deemed necessary with the RCOIC determines that:

- Circumstances exist to justify MaineHealth's participation in the project while still maintaining the protection of human subjects, and
- A conflict management plan is adopted to maintain research integrity and serve the best interests of subjects enrolled in the research. These circumstances and conflict management plans will be documented.

### **25.3.4 Conflict Management Plan**

If MaineHealth's participation in a project is permitted notwithstanding the IFCOI, MaineHealth's participation will be subject to a conflict management plan developed and approved by the IRB as above. In the case of senior administrative officials, the conflict management plan shall be agreed to by the conflicted individual. The IRB has the final authority to determine whether any IFCOI and its management allows the research to be approved. Options for managing institutional conflict of interest, include but are not limited to the following:

- Disclosing the institutional conflict of interest to research subjects in the consent process and documents.

- Disclosing the institutional conflict of interest to any journals or other publications for which the results of the research will be submitted.
- Recusing of conflicted senior administrative officials from scientific merit review of human research
- Having an external, independent IRB review the research in question
- Monitoring of research by independent reviewers
- Divestiture of financial conflicts of interests
- Severance of relationships that create actual or potential conflicts.
- Prohibition of the conduct of the research at the MaineHealth.

### **25.3.5 Timing**

The review, evaluation, and where applicable, management of an IFCOI shall be completed prior to the account establishment of an award for the human subjects' research project or any commencement of the project (including enrollment of any research subjects), whichever comes first. IRB proposals will remain unapproved, pending approval by IRB of the conflict management plan.

### **25.4 Recruitment Incentives**

Payment arrangements between or among sponsors, organizations, investigators, research personnel, 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. Bonus payments do not include payments for bona fide items or services.

## **26 Participant Outreach**

MaineHealth is committed to ensuring that educational opportunities are offered to research participants, prospective research participants, and community members, which will enhance their understanding of human subjects research at MaineHealth and provide them the opportunity to provide input, seek information, and express concerns.

The following procedures describe how MaineHealth fulfills that responsibility.

### **26.1 Outreach Resources and Educational Materials**

1. The ORC dedicates a section of the website to research participants entitled “For Participants.” This website includes resources, such as Frequently Asked Questions (FAQs), brochures, and a listing of relevant research participation-related links.
2. The website includes information regarding how to contact MaineHealth with any questions or concerns about specific research projects or research in general.
3. The website 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. MaineHealth periodically provides presentations related to research to community organizations.
5. The MaineHealth Research Institute (MMCRI) periodically holds “Open Houses” to which members of the public are invited

### **26.2 Evaluation**

On an annual basis, MaineHealth evaluates its outreach activities and makes changes when appropriate. In order to formally evaluate its outreach activities, the ORC Director 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 participants’ website is visited
4. Feedback provided via the “Contact Us” mechanism on the “Participant Outreach Corner”
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.

## 27 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 if the research is subject to the Common Rule, FDA regulations, and/or state laws that provide additional protection for research involving certain categories of health information (such as information derived from HIV/AIDS testing, genetic testing, and mental health records). When research consent is not required by regulation or law (e.g., for exempt research) or the requirement for research consent has been waived by an IRB, the requirements for authorization still apply unless an IRB or Privacy Board has determined that the criteria for a waiver of the authorization requirement are satisfied.

### 27.1 Definitions

**Access.** Access is the mechanism of obtaining or using information electronically, on paper, or other medium for the purpose of performing an official function.

**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.

**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 that includes all of the required elements under the Privacy Rule.

**Covered entity.** A health plan, a health care clearinghouse, or a health care provider who or that 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 disclosed and how it will be protected.

**De-identified.** Data are considered [de-identified under HIPAA](#) when they do not identify an individual, and there is no reasonable basis to believe that the data can be used to identify an individual. The Privacy Rule defines two methods for de-identifying PHI: (1) when the PHI is stripped of all 18 HIPAA-defined identifying elements and the covered entity does not have [actual knowledge](#) that the information could be used alone or in combination with other information to identify an individual who is a subject of the information (Safe Harbor method); or (2) when an appropriate expert determines that the risk is very small that the information could be used, alone or in combination with other reasonably available information, by an anticipated recipient to identify an individual who is a subject of the information (Expert Determination method).

**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, provision of access to, or divulging in any manner, of information outside the entity holding the information.

**Genetic Information.** Genetic information means, with respect to an individual, information about: (i) The individual's genetic tests; (ii) The genetic tests of family members of the individual; (iii) The manifestation of a disease or disorder in family members of such individual; or iv) Any request for, or receipt of, genetic services, or participation in clinical research which includes genetic services, by the individual or any family member of the individual.

Genetic information concerning an individual or family member of an individual includes the genetic information of: (i) A fetus carried by the individual or family member who is a pregnant woman; and (ii) Any embryo legally held by an individual or family member utilizing an assisted reproductive technology. Genetic information excludes information about the sex or age of any individual.

**Genetic services.** A genetic test; genetic counseling (including obtaining, interpreting, or assessing genetic information); or genetic education.

**Genetic test** means an analysis of human DNA, RNA, chromosomes, proteins, or metabolites, if the analysis detects genotypes, mutations, or chromosomal changes. Genetic test does not include an analysis of proteins or metabolites that is directly related to a manifested disease, disorder, or pathological condition.

**Health Information.** Health Information means any information, including genetic 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; or the past, present, or future payment for 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 data sets that exclude 16 categories of direct identifiers that are specified in the Privacy Rule. Limited Data Sets 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, only if the covered entity obtains satisfactory assurances in the form of a Data Use Agreement. Limited Data Sets are not de-identified information under the Privacy Rule.

**Minimum Necessary.** The least PHI 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 PHI 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 protocol 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.** Protected Health Information (PHI) means individually identifiable health information that is 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 (FERPA), as amended, [20 U.S.C. 1232g](#); in records described at 20 U.S.C. 1232g(a)(4)(B)(iv); in employment records held by a covered entity in its role as employer; and regarding a person who has been deceased for more than 50 years.

**Psychotherapy Notes.** Psychotherapy notes means notes recorded (in any medium) by a health care provider who is a mental health professional documenting or analyzing the contents of conversation during a private counseling session or a group, joint, or family counseling session and that are separated from the rest of the individual's medical record. Psychotherapy notes excludes medication prescription and monitoring, counseling session start and stop times, the modalities and frequencies of treatment furnished, results of clinical tests, and any summary of the following items: Diagnosis, functional status, the treatment plan, symptoms, prognosis, and progress to date.

**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 covered 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 a researcher 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.

## **27.2 The IRB's Role under the Privacy Rule**

Under the Privacy Rule, IRBs have 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 the Common Rule and FDA regulations include protections to help ensure the privacy of subjects and the confidentiality of information (as applicable, to research activities that are regulated under those sets of regulations), the Privacy Rule supplements these protections where HIPAA is applicable, 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.

MaineHealth's IRB and, when mutually agreed, the external IRBs it relies upon, fulfill the functions of a Privacy Board for human subject research.

The Privacy Rule does not change the composition of an IRB. When acting upon a request to waive or alter the Authorization requirement, an IRB must follow the procedural requirements of the Common Rule and FDA regulations, if applicable, including using either the normal review procedures (review by the convened IRB) or, as appropriate, 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. DHHS has established categories of research that may be reviewed by an IRB through an expedited review procedure. Expedited review of a request for a waiver or an alteration of the Authorization requirement is permitted if the research study qualifies for expedited review under DHHS requirements. A modification to a previously approved research protocol, 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 all 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:

1. The identity of the approving IRB;
2. The date on which the waiver or alteration was approved;
3. A statement that the IRB has determined that the alteration or waiver or authorization, in whole or in part, satisfies the three criteria in the Rule;
4. A brief description of the PHI for which use or access has been determined to be necessary by the IRB;
5. A statement that the waiver or alteration was reviewed and approved under either normal or expedited review procedures; and
6. The signature of the IRB Chair or other member, as designated by the Chair, of the IRB, as applicable.

MaineHealth will not release PHI to investigators or other third parties without individual authorization or proper documentation of an IRB or Privacy Board approval of a waiver or alteration of the requirement.

### **27.3 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 for research to which the Common Rule, FDA regulations, and/or state laws regarding certain categories of health information apply (although certain research that is subject to the Privacy Rule may be exempt from Common Rule requirements). Just as a valid consent under Common Rule and FDA regulations must meet certain requirements, a valid authorization must be written in plain language and contain certain statements and core elements [45 CFR 164.508.6(c)]. At MaineHealth, the HIPAA authorization is documented within the consent document, and is reviewed along with all other materials submitted for IRB review and approval.

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. See Section 27.12 for more information regarding an individual's right to revoke, procedures, and exceptions.

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 Common rule or FDA 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 (A statement that there is "no expiration date or event" or that authorization expires at the "end of the research study" or "unless and until revoked" by the individual are permissible for research, including authorizations for future research; and
6. The 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 (if such conditioning is permitted under the Privacy Rule), including research-related treatment and consequences of refusing to sign the Authorization; and
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.

#### **27.4 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 alteration must be retained for 6 years from the date of its creation or the date it was last in effect, whichever is later. This is in addition to any other documentation requirements that might apply.

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 the PHI contemplated to be used or disclosed for that 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 some defined group of research purposes, such as accessing PHI for research recruitment purposes. An IRB or Privacy Board may also approve a request that removes some, but not all, required elements or statements of 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, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
  - 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; and
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 IRB or Privacy Board to be used to obtain or release PHI in connection with a multi-site project.

### **27.5 Activities Preparatory to Research**

Under the preparatory to research provision of the Privacy Rule, a covered entity may permit a research to use PHI for purposes preparatory to research such as assessing the feasibility of conducting a research project, developing a grant application or protocol, or identifying potential subjects.

The covered entity must obtain from the investigator representations, either in writing or orally, that (1) the use or disclosure of the PHI is solely to prepare a research protocol or for similar purposes preparatory to research, (2) that the investigator will not remove any PHI from the covered entity (e.g., physically taken out of a facility, or downloaded and retained on the investigator's device) in the course of the review, and (3) the PHI for which access is sought is necessary for the research purpose. [45 CFR 164.512(i)(1)(ii)]

Federal guidance has drawn a distinction between activities that may be undertaken by a researcher who is a member of the covered entity's workforce, e.g., an employee of the covered entity, and a researcher who is not part of the covered entity's workforce. This guidance indicates that researchers may use PHI under the preparatory to research provision to *identify* potential study participants, so long as no PHI is removed from the covered entity and the remaining two representations set forth above can be made. However, the guidance also indicates that researchers may not use PHI obtained pursuant to the "preparatory to research" provision to *contact* potential study subjects unless (i) the researcher is a member of the covered entity's workforce, or (ii) the researcher enters into a BAA with the covered entity. Therefore, if the researcher is not a workforce member or business associate of the covered entity, then the researcher may contact potential subjects only pursuant to a partial waiver of authorization from the cognizant IRB or privacy board, or pursuant to the Authorization of the subject.

MaineHealth further requires that first contact with a patient for recruitment into a study must always be via an MaineHealth individual who has a treatment relationship with that patient. These details, along with approved recruitment tools (e.g., script or flyer etc.) to be used by the individual with the treatment relationship, must be provided in the IRB submission.

### **27.6 Research Using Decedent's Information**

The HIPAA Privacy Rule protects the individually identifiable health information about a decedent for 50 years following the date of death of the individual. When a researcher seeks to use PHI from decedents for a research protocol, the researcher must (1) obtain authorization from the personal representative of the decedent (i.e., the person under applicable law with

authority to act on behalf of the decedent or the decedent's estate), (2) obtain a waiver of the requirement to obtain authorization from an IRB or Privacy Board, or (3) attest to the covered entity holding the PHI that the use or disclosure is solely for research on the PHI of decedents, that the PHI being sought is necessary for the research, and, if requested by the covered entity, provide documentation of the death of the individuals about whom information is being sought.

At MaineHealth, the attestation option referenced above is accomplished by the investigator submitting a Research Use of Decedents' PHI Attestation to the Office of Research Compliance.

## **27.7 Storage and Use of PHI for Future Research**

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. When researchers establish a database or repository containing PHI for the purposes of future research, or intend to maintain the PHI following completion of a primary study for potential future research use, individual authorization for the **storage** of PHI for such future research must be sought unless the IRB has determined that the criteria for a waiver of the authorization requirement are satisfied. See Section 27.4 of this policy manual for a discussion of waivers of authorization.

An authorization for use and/or disclosure of the stored PHI for **future research** must describe the future research uses and/or disclosures in sufficient detail to allow the potential subject to make an informed decision. The Rule does not require that an authorization describe each specific future study if the particular studies to be conducted are not yet determined. Instead, the authorization must adequately describe future purposes such that it would be reasonable for the subject to expect that their PHI could be used or disclosed for such research. When developing the description of potential future research uses, the investigator should be cognizant of uses of information/specimens that the community may consider particularly sensitive, such as genetics, mental health, studies of origin, and use of tissues that may have cultural significance, including whether any state laws may impose additional consent requirements with respect to any of these sensitive categories of information.

The authorization for future research can be a stand-alone document or may be incorporated into the authorization for the establishment of the database or repository or for the primary study, 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 authorization for future research is combined with the authorization for the primary study, the authorization must clearly differentiate between the authorization for the primary study and the authorization for the unspecified future research activities, and allow the subject 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.

It is important to note that securing a HIPAA authorization for unspecified future research activities may not, by itself, satisfy all applicable legal consent requirements. The Common Rule, FDA regulations, and state laws also must be considered, as applicable, in evaluating whether the information (including PHI) or identifiable biospecimens may be used for future research projects.

## 27.8 Corollary and Sub-studies

Consistent with the discussion above relating to future uses of research databases or repositories, the Privacy Rule mandates that subject participation in corollary or sub-studies not essential to the primary aims of the research, such as when PHI from an interventional clinical trial is used to create or to contribute to a central research repository, must be on a voluntary, “opt-in” basis. This is particularly important when the primary research offers a potential direct benefit to the research subject, such as treatment, that might compel the potential subject to agree to an ancillary study, even if the subject would prefer not to do so.

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 (which is one form of “unconditioned activity”), it is acceptable to combine in a single document the authorization for a conditioned activity, such as a clinical trial, with authorization for other forms of unconditioned activities 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 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.

## 27.9 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, because information that has been de-identified consistent with the Privacy Rule requirements is not considered individually identifiable health information. The “Safe Harbor” method permits a covered entity to de-identify data by removing all 18 data elements specified in the Privacy Rule that could be used to identify the individual who is the subject of the information or the individual’s relatives, employers, or household members. To satisfy the Safe Harbor method of de-identification, 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 of the individual or his or her relatives, employers, or household members 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; and
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 the health information could be used, alone or in combination with other reasonably 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 are considered de-identified under HIPAA may still be considered human subject data under the Common Rule and may require IRB review and approval. Removal of HIPAA-identifying elements does not necessarily mean that the identity of the subject is not or may not readily be ascertained by the investigator or associated with the information and thus be considered identifiable private information under the Common Rule. The reverse can also be true (and, in practice, is more likely to occur): information may not be “identifiable” under the Common Rule but, because it contains certain HIPAA identifiers, it is considered identifiable under HIPAA.

### **27.10 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 DUA 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 or disclosure will be made other than as permitted by the DUA or as otherwise required by law, 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 or disclosure, that any agents, including subcontractors, to whom the recipient provides the LDS will agree to the same restrictions and conditions that apply to the recipient, and that the recipient will report any uses or disclosures of the information that they become aware of that are not in keeping with the terms of the DUA. Data Use Agreements for the purposes of research are available through Grants and Contracts.

#### **27.11 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 MaineHealth authorization template.

#### **27.12 Revoking Authorization**

The Privacy Rule establishes the right for an individual to revoke their authorization for uses and disclosures of PHI for research, in writing, at any time, except to the extent that the covered entity has taken action in reliance on the authorization. [45 CFR 164.508(b)(5)] However, individuals providing authorization should be made aware that revoking

authorization does not mean that the individual's PHI may no longer be used in the research or be used or disclosed for other purposes.

At MaineHealth, individuals may revoke authorization by requesting the investigator stop collecting their data. This request may be made by phone, but must also be accompanied by a written request. The investigator will report all subject withdrawals at the time of continuing review. However if the subject withdraws due to an unresolved complaint, or due to an unanticipated problem involving risk to that subject, ORC should be notified as soon as possible in accordance with these SOPs.

A covered entity may continue to use and disclose PHI that was obtained **before** the individual revoked authorization to the extent that the entity has taken action in reliance on the authorization. When the research is being conducted by the covered entity, the covered entity is permitted to continue using or disclosing the **already obtained** PHI to the extent necessary to maintain the integrity of the research (e.g., to account for a subject's withdrawal from a study, to report adverse events, or to conduct an investigation of misconduct). A covered entity may also continue to use the PHI for other activities that are permitted under the Rule without authorization (e.g., health care operations such as QA/QI). Additionally, revoking an authorization does not prevent the continued use or disclosure of PHI by a non-covered entity that had **already received** it pursuant to the authorization.

### **27.13 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 use of that information within the covered entity. A disclosure of PHI means "the release, transfer, provision of access to, or divulging in any manner of information outside of the entity holding the information." 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; or
  - 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; or
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.

## **28 Special Topics**

### **28.1 State-Mandated Reporting**

#### Maine Statute Title 22 §4011-A

Additional information and procedures for reporting are available in MaineHealth Institutional Policy for Reporting of Suspected Child Abuse or Neglect or Drug Affected Baby.

#### Maine Statute Title 22 §3477

Additional information and procedures for reporting are available in MaineHealth Institutional Policy for Reporting Suspected Elder/Adult Abuse, Neglect or Exploitation.

#### Maine Statute Title 22 §821 §822

Additional information and procedures for reporting are available in Department of Health and Human Services, Maine Center for Disease Control and Prevention, Chapter 258: Rules for the Control of Notifiable Diseases and Conditions.

### **28.2 Certificates of Confidentiality**

Certificates of Confidentiality (CoC) protect research information by prohibiting certain disclosures and conditioning others upon consent from the subject. The protections and requirements of CoCs are outlined in 42 U.S.C. 241(d) and in written policies and requirements of certain federal agencies such as NIH and CDC, and are summarized below.

CoC's are obtained as follows:

- CoCs are issued automatically when research is conducted or supported by NIH and falls within the scope of the NIH policy.
- CoCs are issued automatically when research is conducted or supported by the [CDC and involves the collection of identifiable, sensitive information](#)
- Research that is not supported by NIH or CDC may still have the protections afforded by CoCs through successful application to the NIH, FDA, HRSA, SAMHSA or other authorized Federal agencies or departments.

Additional information about CoCs and the application process for non-NIH research is available on the NIH CoC Website.

#### **28.2.1 Definitions**

Identifiable, sensitive information means information that is about an individual and that is gathered or used during the course of biomedical, behavioral, clinical, or other research and

1. Through which an individual is identified; or

2. For which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual.

### **28.2.2 Protections and Requirements**

When a CoC is issued, whether automatically or under an approved application, the person(s) engaged in the research must not disclose or provide the name of a subject or any information, document, or biospecimen that contains identifiable, sensitive information about the subject and that was compiled for the purposes of the research:

1. In any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, unless the disclosure is made with the consent of the individual to whom the information, document, or biospecimen pertains; or
2. To any other person not connected with the research, unless:
  - a. Required by Federal, State, or local laws (e.g., adverse event reporting to the FDA, transmissible disease reporting required under State law), but excluding proceedings as described in “1” above;
  - b. Necessary for the medical treatment of the subject to whom the information, document, or biospecimen pertains and made with the consent of the subject;
  - c. Made with the consent of the individual to whom the information, document, or biospecimens pertains; or
  - d. Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.

### **Additional Protections**

Identifiable, sensitive information protected under a CoC, and all copies thereof, are immune from the legal process, and shall not, without the consent of the of the individual to whom the information pertains, be admissible as evidence or used in any action, suit, or other judicial, legislative, or administrative proceeding.

Identifiable, sensitive information that has been collected under a CoC, and all copies thereof, are protected for perpetuity.

Nothing in the rule (42 U.S.C. 241(d)) may be construed to limit the access of a subject to information about himself or herself collected during the research.

When consent is obtained, the consent must inform subjects that a CoC is in place and describe the protections and limitations.

### **28.2.3 NIH Policy**

The NIH Policy on CoCs applies to “all biomedical, behavioral, clinical, or other research funded wholly or in part by the NIH, whether supported through grants, cooperative agreements, contracts, other transaction awards, or conducted by the NIH Intramural Research Program,

that collects or uses identifiable, sensitive information” that was commenced or ongoing on or after December 13, 2016.

The [CDC requirements for CoCs](#) apply to “*CDC supported research commenced or ongoing after December 13, 2016 and in which identifiable, sensitive information is collected, as defined by Section 301(d).*”

CoCs are automatically granted, and the requirements of such must be complied with, whenever an NIH or CDC-funded activity falls within the scope of the policy. Investigators and institutions are responsible for determining when research with NIH or CDC support are covered by a CoC.

NIH and CDC expand upon 42 U.S.C. 241(d) by explaining that NIH and CDC consider research in which identifiable, sensitive information is collected or used, to include:

- Human subjects research as defined in 45 CFR 46, including research determined to be exempt (except for exempt research when the information obtained is recorded in such a manner that human subjects cannot be identified or the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects);
- Research involving the collection or use of biospecimens that are identifiable to an individual or for which there is at least a very small risk that some combination of the biospecimen, a request for the biospecimen, and other available data sources could be used to deduce the identity of an individual;
- Research that involves the generation of individual level, human genomic data from biospecimens, or the use of such data, regardless of whether the data is recorded in such a manner that human subjects can be identified or the identity of the human subjects can readily be ascertained; or
- Any other research that involves information about an individual for which there is at least a very small risk, as determined by current scientific practices or statistical methods, that some combination of the information, a request for the information, and other available data sources could be used to deduce the identity of an individual, as defined in subsection 301(d) of the Public Health Service Act.

#### **28.2.4 NIH and CDC CoC Determination**

At MaineHealth, Grants and Contracts staff will, in consultation with the investigator(s) (or Program or Project Director, if applicable), determine if the NIH policy or CDC requirements applies to research with NIH or CDC involvement or support. The questions outlined in the NIH policy and CDC requirements will be used to guide the analysis. When it has been determined that the NIH policy or CDC requirements don’t apply, investigators (or Program or Project Directors, if applicable) are responsible for consulting with Grants and Contracts staff whenever they are proposing changes to the NIH or CDC supported activity that may impact or change the analysis.

The NIH policy and CDC requirements include additional responsibilities and requirements for internal controls and for ensuring that recipients of identifiable, sensitive information protected

by a CoC understand that they are also subject to the requirements of subsection 301(d) of the Public Health Service Act.

### **28.2.5 Application Procedures for non-NIH, non-CDC Research**

Any person engaged in human subjects research that collects or uses identifiable, sensitive information may apply for a CoC. For most research, CoCs are obtained from NIH. An investigator may apply for a CoC through the NIH Institute or Center funding research in a scientific area similar to the project.

When a researcher is conducting a research project that is covered by the Agency for Healthcare Research and Quality (AHRQ) confidentiality statute ([42 U.S.C. section 299c-3\(c\)](#)), a CoC is not needed ([AHRQ notice NOT-HS-18-012](#)). While the AHRQ statute does not define “identifiable”, AHRQ applies the PHS Act definition of “identifiable, sensitive information”. Investigators should consult with AHRQ when they believe that data might be considered “non-identifiable” or when otherwise uncertain whether a research project falls within the scope of the statute.

When a researcher is conducting a research project that is covered by the Department of Justice (DoJ) [confidentiality statute](#), [28 CFR 22](#), and/or a [NIJ Privacy Certificate](#), a CoC may not be needed. Investigators should consult with DoJ/NIJ to determine whether a CoC should be obtained.

If there is an Investigational New Drug Application (IND) or an Investigational Device Exemption (IDE), the sponsor can request a CoC from the FDA. When FDA funds or conducts research, a CoC is automatically issued.

CoCs may also be issued by other Federal agencies and departments, such as SAMSHA, or HRSA. For more information, see the NIH CoC Website.

### **28.2.6 IRB Review**

Investigators are responsible for clearly representing in the IRB submission that a CoC is in place, or that an application for CoC has been submitted. For the latter case (non-NIH funded), when the CoC application is in process or pending, the IRB may condition final approval upon its receipt.

For studies that are already underway, investigators must submit a Modification Request in IRBNet, along with updated consent language (if applicable), when a CoC is applied for, or when automatically issued under the NIH policy or CDC requirements.

When reviewing research under a CoC, the MaineHealth IRB will evaluate whether the research plan is consistent with the obligations to protect information and specimens under a CoC and whether the consent language, if applicable, discloses the CoC and appropriately describes the associated protections and limitations. Sample consent language is available on the NIH CoC Website and is available in the template consent forms found in IRBNet and MaineHealth’s ORC website.

When research is not under a CoC, the IRB may require an investigator to apply for a CoC if the research includes identifiable, sensitive information and the IRB determines that a CoC is necessary to minimize risks and adequately protect subjects' privacy and the confidentiality of subjects' information or specimens.

### **28.3 Databases, Registries, & Repositories**

Databases, registries, and biospecimen repositories (all referred to as repositories throughout this section) are used to store data and/or biospecimens for future use.

There are two types of repositories:

- Non-research repositories created and maintained for purposes that are 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. Non-research repositories that are altered to facilitate research (e.g., through the addition of data fields not necessary for the core purpose of the repository) are considered research repositories.

#### **28.3.1 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 approval is required for the research use of identifiable private information or identifiable human specimens from non-research repositories, and, regardless of identifiability, when specimens will be used to evaluate the safety or effectiveness of a medical device. Research under the auspices of MaineHealth that includes the use of coded private information or specimens, must either be submitted for IRB review or for a "Human Subjects Research Determination" (See Section 4).

Researchers submitting an application for research using data or specimens from non-research repositories must describe the source of the data/specimens and any terms, conditions, or restrictions on use. Data/specimens cannot be used for research if the person from whom the data/specimens originated objected to its use for research. Informed consent and HIPAA authorization (when applicable) must be obtained unless the IRB determines that the criteria for a waiver are satisfied.

#### **28.3.2 Research Repositories**

Research repositories involve three distinct activities:

1. Collection of data/specimens;

2. Storage and management of data/specimens; and
3. Distribution of data/specimens.

### **Collection**

Informed consent and HIPAA authorization (when applicable) must be obtained unless the IRB determines that the criteria for a waiver are satisfied.

Informed Consent information should include:

- A clear description of
  - What data/specimens will be collected;
  - Where the data/specimens will be stored, who will have access, and how the data/specimens will be secured;
  - Whether the data/specimens will be identifiable, coded, or deidentified;
  - The types of research to be conducted and any limitations or restrictions on such; and
  - The conditions under which data/specimens will be released to recipient-investigators
- 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 and how to make such a request)
- When appropriate, the plan for management of incidental findings and sharing of results

### **Storage and Management**

Repositories should have written policies describing:

- The conditions under which data/specimens will be accepted (e.g., inclusion criteria)
- Informed consent
- IRB review
- The sources of data/specimens
- Whether data/specimens will be identifiable, coded, or de-identified, and, if coded, management of the linkage key; and
- Physical and procedural mechanisms for the secure receipt, storage, and distribution of data/specimens

### **Distribution**

Repositories should have written policies describing:

- How data/specimens may be requested and by whom

- Any requirements associated with a request for data/specimens (e.g., verification of IRB approval or that approval is not required)
- Any limitations or restrictions on how data/specimens may be used
- Whether released data/specimens will be identifiable, coded, or de-identified, and, if coded, any circumstances under which recipient investigators will have access to or be provided with the key or other means to re-identify; and
- Agreements with recipient investigators specifying the terms of use.

### **28.3.3 IRB Oversight**

IRB approval is required for the establishment and operation of a research repository when the data/specimens that are accessed, received, stored, or distributed are identifiable. In general, private information or specimens are considered individually identifiable when the identities of the subjects are known to investigators/repository operators or when the data/specimens can be linked to specific individuals either directly or indirectly through coding systems.

Separate IRB approval is required for the use of data/specimens from a repository when the recipient investigator(s) know or may readily ascertain the identity of individual subjects, and, regardless of identifiability, when specimens will be used to evaluate the safety or effectiveness of a medical device. Research under the auspices of MaineHealth that includes the use of coded private information or specimens, must either be submitted for IRB review or for a “Human Subjects Research Determination” (See Section 4). The only exception to this policy is when the coded private information or specimens are to be obtained from an IRB-approved repository and the rules of that repository forbid the release of identifiable information, the release of the key to the code or other means that would allow re-identification, or the release of sufficient information that investigators could readily ascertain the identity of subjects.

### **28.4 Research Involving or Generating Genetic Information**

Research that generates or uses genetic information 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, and may result in stigmatization and discrimination. Information about one's own genetic make-up may also provide information about family members.

In studies involving genetic testing or analysis of genetic information, several questions should be addressed to ensure that potential risks are well understood and that the rights and interests of subjects and their family members are carefully considered and planned for. For example:

1. Is the testing intrinsic to the study? If not, has participation in the genetic testing component been provided as an opt-in?
2. Will test results be given? Is there an appropriate plan for return of results?

3. Does the subject or family member be provided the option to receive or not receive results? How will this decision be recorded?
4. Could the results provide information about individual disease risk? Disease risk for family members?
5. Could other clinically relevant information or incidental findings be uncovered by the study? Is there a plan for the management of such findings?
6. Will testing that could produce clinically relevant information occur in a CLIA-certified lab? If not, are there tests available that could validate or support findings?
7. Could a change in a family relationship be disclosed, such as mistaken paternity?
8. Could/will the research provide information about the origins, ancestry, or natural history of families, indigenous peoples, tribal populations, or other populations? What are the possible risks?
9. Could/will the research generate information that could place subjects or family members at risk or be stigmatizing?
10. Could/will the research generate information of other value or importance to subjects/families?
11. Do any practical limitations exist on the subject's right to withdraw from the research, withdraw data, and/or withdraw biological materials (e.g., specimens, cell lines, extracted genomic DNA)?
12. How will the information and/or biological materials be protected and who will have access?
13. What is the potential for re-identification of individual subjects (e.g., through the combination of their genetic information and/or materials with other sources of information (e.g., public records))? What measures can be taken to mitigate these risks?
14. Is a Certificate of Confidentiality (CoC) in place or should one be considered? (See Section 28.2)
15. Will the specimens, cell lines, or genetic information be stored and/or made available for future research? Is this provided as an opt-in when not intrinsic to the study? (See Section 27.7)

Investigators should carefully consider the above and other factors relevant to their specific study when developing the protocol, consent process, and consent form. The President's Bioethics Commission, the National Academies of Sciences, Engineering, and Medicine, and others have produced reports, recommendations, and materials that investigators and the IRB may find helpful in protocol development and review, including:

- [Returning Individual Research Results to Participants: Guidance for a New Research Paradigm](#)

- [Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts](#)
- [Privacy and Progress in Whole Genome Sequencing](#)
- [Genetics Research and American Indian and Alaska Native Communities](#)
- National Human Genome Research Institute:
  - [Human Subjects Research in Genomics](#)
  - [Return of Research Results](#)
  - [Data Sharing and Privacy](#)
  - [Informed Consent for Genomics Research](#)

In addition to the ethical considerations, investigators must ensure that research involving genetic testing or use of genetic information is consistent with applicable law (e.g., GINA, HIPAA, EU GDPR, state law) and policy (e.g., NIH).

#### **28.4.1 Genetic Information Nondiscrimination Act (GINA)**

[GINA](#) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against individuals based on their genetic information. This law protects individuals, including research subjects, in the following ways:

- Health insurance companies and health plans are generally prohibited from requesting or requiring genetic information of an individual or their family members, including genetic information generated from research;
- If health insurance companies and health plans do receive such genetic information, they may not use it to make decisions regarding coverage, rates, or preexisting conditions; and
- Employers with 15 or more employees generally may not use genetic information for hiring, firing, promotion, or other decisions regarding terms of employment.

GINA's protections do not extend to life insurance, disability insurance, or long-term care insurance.

GINA defines genetic information as information about:

- An individual's genetic tests;
- Genetic tests of an individual's family members;
- Genetic tests of any fetus of an individual or family member who is a pregnant woman, and genetic tests of any embryo legally held by an individual or family member utilizing assisted reproductive technology;
- The manifestation of a disease or disorder in an individual's family members (family history); or
- Any request for, or receipt of, genetic services or participation in clinical research that includes genetic services (genetic testing, counseling, or education) by an individual or an individual's family members.

GINA includes a “research exception” that allows health insurers and health plans who are engaged in research to request, but not require, that an individual undergo a genetic test so long as certain requirements are satisfied. Additional information on GINA and this exception are available on this [OHRP website](#).

The MaineHealth IRB will consider the protections and limitations of GINA when it assesses the risks of research generating or using genetic information and the adequacy of the measures to protect privacy and maintain confidentiality. Generally, the IRB will also require that the protections and limitations of GINA are disclosed in the consent process when applicable. Sample language for GINA is provided in MaineHealth’s template consent form.

### **28.5 Genomic Data Sharing (GDS)**

MaineHealth complies with the [NIH GDS Policy](#), which allows for “broad and responsible sharing of genomic research data”, via submission of said data into an NIH-designated data repository. The intent of NIH’s policy is to speed discoveries to diagnose, treat, and prevent disease. To ensure consistency in the protection of human subjects, MaineHealth applies the NIH principles for informed consent and for a genomic data sharing plan to all research that involves or contemplates genomic data sharing.

The NIH policy applies to grant activities requesting support from NIH for research involving the generation of large-scale human (and/or non-human) genomic data, regardless of funding level, such as:

- Research project grants (Rs);
- Program projects (Ps) and SCORs (Ss);
- Cooperative agreements for research (Us);
- Individual career development awards (Ks) that include a research component;
- S activities that include a research component; and
- All other activities that include a research component.

Also covered under this policy is research involving data derived from these activities for subsequent research. All basic and clinical research, including clinical trials, supported by NIH that involves the generation or use of large-scale genomic data fall within the scope of the policy.

The policy does not apply to:

- Institutional training grants (T32s, T34s, T35s, and TL2s);
- K12 career development awards (KL2s);
- Individual fellowships (Fs);
- Resource grants and contracts (Ss);
- Linked awards derived from previously reviewed applications (KL1, KL2, RL1, RL2, RL5, RL9, TL1, UL1);

- Facilities or coordinating centers funded through related initiatives to provide genotyping, sequencing, or other core services in support of GDS.

Because of the potential for re-identification of genomic data, Certificates of Confidentiality (CoCs) are automatically issued by the NIH for any research it supports, in part or in whole, that involves *“the generation of individual level, human genomic data from biospecimens, or the use of such data, regardless of whether the data is recorded in such a manner that human subjects can be identified or the identity of the human subjects can readily be ascertained as defined in the Federal Policy for the Protection of Human Subjects (45 CFR 46).”* Research covered by the [NIH policy](#) and/or the underlying [PHS Act](#) is protected by the CoC in perpetuity; as such any downstream recipients of such information must comply with the requirements of the PHS Act.

Investigators without NIH support who intend to submit genomic data to a NIH repository are encouraged to obtain a CoC.

For more information on CoCs, see Section 28.2.

### 28.5.1 Definitions

**Genomic data:** information derived from study of an organism’s genome, i.e., the set of DNA (including all the genes within) in every cell that provides all of the information needed to build and maintain that organism.

**Genomic Summary Results (GSR):** GSR (also referred to as “aggregate genomic data” or “genomic summary statistics”) are results from primary analyses of genomic research that convey information relevant to genomic associations with traits or diseases across datasets rather than associations specific to any one individual research participant (e.g., genotype counts and frequencies; allele counts and frequencies; effect size estimates and standard errors; likelihood; and p-values). **Sensitive GSR** refers to GSR where the privacy risks may be heightened for study populations (e.g., populations from isolated geographic regions or with rare traits) or the study populations may be more vulnerable to group harm (e.g., because the data includes potentially stigmatizing traits). Information regarding NIH’s updated policy on the access, use, and management of GSR may be found here:

<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-19-023.html>

**Large-scale data** include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data. Examples of genomic research projects that are subject to the Policy and the timeline for submission and sharing of data from such projects may be found here:

[https://osp.od.nih.gov/wp-content/uploads/Supplemental\\_Info\\_GDS\\_Policy.pdf](https://osp.od.nih.gov/wp-content/uploads/Supplemental_Info_GDS_Policy.pdf)

**NIH-Designated Data Repository:** any data repository maintained or supported by NIH either directly or through collaboration. Examples of such repositories is available here:

<https://osp.od.nih.gov/scientific-sharing/data-repositories-and-trusted-partners/>. Data may be unrestricted or controlled access:

- **Unrestricted-Access (“Open Access”):** data are publicly available to anyone (e.g., The 1000 Genomes Project). Non-sensitive GSR are made available through unrestricted access.
- **Controlled-Access:** the data are available to an investigator for a specific project only after the investigators and institution certify to abide by specified terms and conditions and NIH has approved the use. Sensitive GSR are made available through controlled access.

## 28.5.2 Procedures

### IRB Submissions and GDS

For any cell lines created or specimens to be collected, analyzed, and shared subject to the GDS Policy, the IRB expects that informed consent will be obtained from the research subject for the future research uses and broad sharing of data required under the policy. **This is the case even if the specimens or cell lines are de-identified.** If there are compelling scientific or legal reasons that necessitate the use of genomic data from cell lines or clinical specimens that lack consent for research use and data sharing, investigators will need to provide a justification in the funding request to NIH for their use. The funding NIH institute/center will review the justification and decide whether to make an exception to the consent expectation. Exceptions from the NIH are not required if only some participants decline to consent to broad sharing, rather an exception request must be granted by NIH for research when consent for broad sharing has not or will not be sought.

Subjects asked to allow for future research uses and broad sharing of their genomic data have the ability to decline, and still remain in the research (however their data cannot be placed into a repository or otherwise broadly shared). The only exception to this is when sharing of the data is intrinsic to the study (e.g., the purpose of the study is to establish a repository for sharing biological specimens and/or data for future research).

Sample consent language for studies subject to GDS is available in the consent template in IRBNet. [NIH](#) and [NHGRI](#) also provides guidance and resources to assist in the development of appropriate consent forms for research involving or generating genetic or genomic data.

Applications to the NJH IRB should include information about the proposed generation or use of genomic data including, as applicable:

- Whether the research will generate or use data subject to the NIH GDS policy;
- The name of the [NIH data repository/database](#), or other repository or database, that data will be submitted to or acquired from;
- Whether the data is or should be classified as restricted access or unrestricted access;
- Whether the data is or should be classified as sensitive (e.g., studies involving populations from isolated geographic regions or with rare traits, studies that include data on potentially stigmatizing traits, etc.)

- Whether there are any data use limitations or modifiers (e.g., use limited to a specific disease, restricted to not-for-profit organizations, IRB approval requirement, etc.);
- The plan for informed consent and the proposed consent language;
- Supplement J – Storing Data or Specimens for Future Use; and
- A copy of the genomic data sharing plan.

The IRB will review the proposal for genomic data sharing or subsequent use of such genomic data in accordance with the criteria for approval

### Grant Applications and GDS

Investigators planning to apply to NIH for research that will generate large-scale human genomic data as defined above should contact the appropriate NIH Program/Project officials to discuss expectations and timelines for complying with this policy. Along with the grant, the following will need to be submitted:

- **Notification in a cover letter** of the intent to generate large-scale human genomic data
- **A genomic data sharing plan**, within the grant’s resource sharing plan section (NIH guidance on these plans is available here: [https://osp.od.nih.gov/wp-content/uploads/NIH\\_Guidance\\_Developing-GDS\\_Plans.pdf](https://osp.od.nih.gov/wp-content/uploads/NIH_Guidance_Developing-GDS_Plans.pdf) )
- **Institutional Certification** from Grants and Contracts (template available here: [https://osp.od.nih.gov/wp-content/uploads/GDS\\_Extramural\\_Certification.pdf](https://osp.od.nih.gov/wp-content/uploads/GDS_Extramural_Certification.pdf) ). Certification must be provided for all sites contributing samples. If more than one site is contributing samples, the primary site may submit one certification on behalf of all collaborating sites (or each site may provide their own certification if this is the site’s preference). This certification assures that:
  - The data submission is consistent with applicable national, tribal, and state laws and regulations, and institutional policies;
  - Any limitations on the research use of the data, as expressed in the informed consent documents, are delineated within the certification;
  - The identities of research participants will not be disclosed to the repositories;
  - An IRB and/or Privacy Board has reviewed the investigator’s proposal for data submission and assures that:
    - the protocol for the collection of genomic and phenotypic data is consistent with 45 CFR 46;
    - data submission and subsequent data sharing for research purposes are consistent with the informed consent of study participants from whom the data were obtained;
    - consideration was given to the risks to individual participants and their families associated with data submitted to the repositories and subsequent sharing, including unrestricted access to GSR; and
    - the investigator’s plan for de-identifying datasets is consistent with the standards outlined in the NIH Genomic Data Sharing (GDS) Policy.

- **In situations where the sharing of human data is not possible** (i.e., the Institutional Certification criteria cannot be met), a justification is required to explain why these data cannot be shared, and an alternative data sharing plan will need to be provided. Exceptions to NIH expectations for data submission to an NIH-designated data repository will be considered on a case-by-case basis by the NIH funding Institute or Center (IC).

Investigators who wish to use controlled-access human genomic data from NIH-designated data repositories (e.g., dbGaP) should briefly address their plans for requesting access to the data and state their intention to abide by the NIH Genomic Data User Code of Conduct in the Research Plan of the application. The code of conduct is available here:

[https://osp.od.nih.gov/wp-content/uploads/Genomic\\_Data\\_User\\_Code\\_of\\_Conduct.pdf](https://osp.od.nih.gov/wp-content/uploads/Genomic_Data_User_Code_of_Conduct.pdf).

Access to controlled-access data is dependent on an approval process that involves the relevant NIH Data Access Committee(s). Applicants may wish to secure access to the data prior to submitting their application for NIH support. Secondary users of controlled-access data are not expected to deposit their findings into NIH-designated data repositories, unless appropriate.

Investigators who wish to use/download data NIH unrestricted-access repositories, including non-sensitive GSR should not attempt to identify individual human research participants from whom the data were obtained, and, in all oral and written presentations, disclosures, or publications, acknowledge the specific dataset or accession numbers and the repository through which the data were accessed.

Procedures for submitting data into, or requesting access for data from an NIH-designated repository, are available here: <https://osp.od.nih.gov/scientific-sharing/researchers-institutional-certifications/>.

## **28.6 Department of Defense**

Research conducted or supported by the Department of Defense (DoD Research) 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). Support of a study generally means the provision of funding, personnel (both military and civilian DoD employees), facilities, and any other resources.

DoD components (e.g., Army, Navy) may have additional requirements. The PI and a representative of the HRPP or IRB should contact the Human Research Protection Official (HRPO) for the DoD Component conducting or supporting the research. In most cases, protocols will also require review, approval and oversight by the DoD component HRPP. DoD review must be conducted before research involving human subjects can begin. The HRPO provides administrative review and approval to confirm the research is compliant with federal and DoD requirements.

MaineHealth 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”

It is the responsibility of the PI to ensure compliance with DoD requirements for human subject protection. IRB staff, chairs and members will use these SOPs, DoDD 3216.02, the DoD Reviewer Checklist, and any relevant DoD component-specific instructions or materials to guide the IRB review and oversight of DoD research.

### **28.6.1 Key DoD Standards and Requirements**

#### **28.6.1.1 Minimal Risk**

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*” may 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).

#### **28.6.1.2 Education and Training**

All personnel involved in the conduct of DoD research must complete initial and continuing education in the protection of human subjects as described in this manual. Personnel must also familiarize themselves with DoD’s specific requirements by reviewing these SOPs, DoDD 3216.02, and any relevant materials specific to the DoD component. The DoD component may require additional education and/or certification to ensure that personnel are qualified to

perform the research. The DoD component may evaluate the training policies of MaineHealth to ensure the personnel are qualified to perform the research, based on the complexity and risk of the research.

### **28.6.1.3 Appointment of a Research Monitor**

When DoD research involves **more than minimal risk**, the IRB **will** require and approve an independent research monitor by name. When research involves no more than minimal risk, an investigator may identify a research monitor, or the IRB or IO may appoint a monitor. 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 and the IRB or a HRPP official shall communicate 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. The monitor:

- May perform oversight functions (e.g. observe recruitment, enrollment procedures, and the consent process, oversee study interventions and interactions, review monitoring plans and reports of 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.
- The research monitor has the authority to stop a research study in progress, remove individual subjects from the study, and to take whatever steps are necessary to protect the safety and well-being of participants until the IRB can assess the monitor's report.
- Research monitors are obligated to promptly report their observations and findings to the IRB or other designated official.

### **28.6.1.4 Additional protections for vulnerable subjects**

Non-exempt research involving **pregnant women, fetuses, or neonates** as subjects must meet the requirements of Subpart B of the Common Rule, with the following modifications:

- The applicability of Subpart B is limited to non-exempt research involving:
  - Pregnant women as human subjects involved in research that is more than minimal risk and that includes interventions or invasive procedures to the woman or the fetus; or
  - Involving fetuses or neonates as subjects.
- For purposes of applying Subpart B, the phrase "biomedical knowledge" will be replaced with "generalizable knowledge."

- Fetal research must comply with the US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g.

Research involving **prisoners** as subjects must meet the requirements of Subpart C of the Common Rule, with the following modifications:

- 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. The prisoner representative may be a prisoner, an employee of the prison, or an individual not affiliated with the prison.
- In addition to the four allowable categories of research involving prisoners in Subpart C, two additional categories are allowable:
  - Epidemiological research that meets the following criteria:
    - 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.
    - Prisoners are not a particular focus of the research
  - Research that would meet the criteria for exemption described at 32 CFR 219.101(b), can be conducted but must be approved by a convened IRB and meet the requirements of subpart C, DoDD 3216.02, and other applicable requirements.
- When a previously enrolled human subject becomes a prisoner and the research was not previously approved for the inclusion of prisoners:
  - The PI must promptly notify the IRB.
  - If the PI asserts to the IRB that it is in the best interest of the prisoner to continue to participate in the research while a prisoner, the IRB Chair may determine that the prisoner may continue to participate until the convened IRB can review the request to approve a change in the research protocol and until the IO and DoD Component office review the IRB's approval to change the research protocol. Otherwise, the IRB Chair will require that all research interactions and interventions with the prisoner (including obtaining identifiable private information) cease until the convened IRB can review the request to approve a change in the research protocol.
  - The convened IRB, upon receipt of notification that a previously enrolled human subject has become a prisoner, will 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 can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner's confinement does not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research from continuing as approved, the convened IRB may approve a change in the study to allow the prisoner to continue to participate in the research. This approval is limited to the individual prisoner-subject and does not allow recruitment of prisoners as participants.

- This type of request for change in the research protocol cannot be reviewed and approved by expedited review. The research does not have to meet one of the six allowable DoD categories for research involving prisoners.
- MaineHealth will promptly report all decisions in this matter to the component HRPO. The HRPO must concur with the IRB decisions before the human subject can continue to participate while a prisoner.

Research involving **Children** as subjects must meet the requirements of Subpart D of the Common Rule, including that:

- 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 **Military Personnel** as subjects must meet the following requirements:

- Service members must 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.
- Superiors of Service members (e.g., unit officers, senior NCOs, and equivalent civilians) in the chain of command must not be present at any human subject recruitment sessions or during the consent process in which members of units under their command are afforded the opportunity to participate as research subjects. When applicable, the superiors so excluded shall be afforded the opportunity to participate as research subjects in a separate recruitment session.
- When research involving Service members is greater than minimal risk and recruitment occurs in a group setting, the IRB will appoint an ombudsman. The ombudsman must not be associated in any way to the research and must be present during the recruitment to monitor that the voluntary involvement or recruitment of the Service members is clearly and adequately stressed and that the information

provided about the research is clear, adequate, and accurate. The ombudsman may also be the research monitor.

Research involving **DoD Civilians** as subjects must meet the following requirements:

- DoD Civilians must follow their organization’s policies regarding the requirement to obtain permission to participate in research
- Supervisors (e.g., military and civilian supervisors or anyone in the supervisory structure) are prohibited from influencing the decisions of their subordinates regarding participation as subjects in research
- Supervisors (e.g., military and civilian supervisors or anyone in the supervisory structure) must not be present at any human subject recruitment sessions or during the consent process in which DoD civilians under their supervision are afforded the opportunity to participate as human subjects. When applicable, supervisors so excluded shall be afforded the opportunity to participate as human subjects in a separate recruitment session
- For research involving civilians as human subjects when recruitment occurs in a group setting, the IRB will discuss appointing an ombudsman. The decision to require the appointment of an ombudsman should be based in part on the human subject population, the consent process, and the recruitment strategy.

Research involving **other vulnerable populations** must meet the following requirements:

- Investigators, IRBs, and IOs will consider the need for appropriate similar safeguards for other vulnerable populations, such as: research involving human subjects and investigators in supervisor-subordinate relationships, human subjects with decisional or mental impairments, human subjects with a physical disability, or any other kind of human subjects in circumstances that may warrant provision of additional protections. As appropriate, qualified individuals (e.g., research monitors, ombudsmen, advocates) may be appointed to perform oversight functions or assist the human subjects.

#### **28.6.1.5 Limitation of Waivers and Exceptions from Informed Consent**

For DoD-funded research, if the research meets the definition of “*research involving a human being as an experimental subject,*” informed consent must be obtained in advance from the experimental subject or their LAR if the subject cannot consent. If consent is to be obtained from a LAR, the IRB must determine that the research intends to benefit the individual subject.

The Assistant Secretary of Defense for Research and Engineering may waive the requirements for consent when all of the following are met:

1. The research is necessarily to advance the development of a medical product for the Military Services;
2. The research may directly benefit the individual experimental subject; and
3. 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 living individual 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.

An exception from consent in emergency medicine research is prohibited unless a waiver is obtained from the Secretary of Defense.

#### **28.6.1.6 Limitations on Compensation for Human Subjects in Research**

DoDD 3216.02 describes allowable and prohibited compensation for human subjects participating in DoD research and for Federal personnel such as civil servants and Service members. These provisions are intended to ensure compliance with the Dual Compensation Act and 24 U.S.C. 30. Summarized:

- Federal personnel while on duty and non-Federal personnel may be compensated for blood collections for research up to \$50 for each blood collection
- Federal personnel are prohibited from receiving pay or compensation for research during duty hours (except for blood collection as noted above)
- Non-Federal personnel may be compensated for research participation other than blood collections in a reasonable amount, as approved by the IRB according to local prevailing rates and the nature of the research
- Federal personnel may be compensated for research if the participant is involved in the research when not on duty in the same way as human subjects who are not Federal personnel (i.e., compensated for participation in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research). However, payment to off-duty Federal personnel for research participation other than blood draws must not be directly from a Federal source (payment from a Federal contractor or other non-Federal source is permissible)

Additional detail is available in DoDD 3216.02 or by consulting the component HRPO.

#### **28.6.1.7 Reporting Requirements**

The Institution must 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 unanticipated problems involving risks to subjects or others, suspensions, terminations, and serious or continuing noncompliance regarding DoD-supported research involving human subjects.

### **28.6.1.8 Recordkeeping Requirements**

Recordkeeping requirements for DOD-supported research with human subjects are longer than the Common Rule's requirement. DOD may require submitting records to DOD for archiving. Investigators should consult with the HRPO regarding record-keeping requirements for their research.

Records must be made accessible for inspection and copying by representatives of the DoD at reasonable times and in a reasonable manner as determined by the supporting DoD component. The fact that DoD may inspect records should be disclosed in the consent process.

### **28.6.1.9 Addressing and Reporting Allegations of Non-Compliance with Human Research Protections**

MaineHealth must report the initiation of all investigations of allegations of non-compliance and report the results of all such investigations (regardless of the findings) to the HRPO.

### **28.6.1.10 Addressing and Reporting Allegations of Research Misconduct**

MaineHealth will adhere to the requirements of DODD 3210.7 and the terms of any DoD award when allegations or findings of research misconduct arise.

### **28.6.1.11 Additional Requirements for DoD Research**

IRB review must consider the scientific merit of the research. The IRB may rely on outside experts to provide an evaluation of scientific merit.

When conducting research with international populations, additional safeguards for research conducted with international populations the organization or researcher must have permission to conduct research in that country by certification or local ethics review. Researchers must follow all local laws, regulations, customs, and practices.

Disclosure regarding the provisions for research-related injury must follow the requirements of the DoD component.

Surveys performed on DoD personnel must be submitted, reviewed, and approved by the DoD component HRPO after the research protocol is reviewed by the IRB. When a survey crosses DoD components, additional review may be required by DoD.

When any institution relies upon another institution's IRB for DoD research, there must be a written agreement defining the responsibilities and authorities of each organization in complying with the terms of each institution's Federal assurance and DoDD 3216.02.

When conducting multi-site or collaborative research, a formal agreement between organizations is required to specify the roles and responsibilities of each party.

Civilian researchers attempting to access military subjects should seek collaboration with a military researcher familiar with service-specific requirements.

## 28.7 ICH-GCP E6

When MaineHealth commits to comply with ICH-GCP E6 as a term of a grant or contract, investigators and the IRB take on additional responsibilities. Investigators are responsible for clearly indicating within their IRB application materials that proposed research is subject to ICH-GCP E6 and for attesting to compliance with ICH-GCP E6 requirements. The MaineHealth IRB will evaluate compliance with the aid of a checklist and by consulting the current guidance [E6\(R2\) Good Clinical Practice: Integrated Addendum to ICH E6\(R1\)](#) posted by the FDA on its website. MaineHealth does not require or evaluate compliance with ICH-GCP E6 requirements that are not consistent with FDA regulations (for example, requiring the reporting to the IRB of all adverse drug reactions that are both serious and unexpected instead of requiring the reporting of unanticipated problems involving risks to subjects or others).

### 28.7.1 IRB Responsibilities

1. An IRB should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects;
2. The IRB/IEC should obtain the following documents:
  - a. Trial protocol(s)/amendment(s);
  - b. Written informed consent form(s) and consent form updates that the investigator proposes for use in the trial;
  - c. Subject recruitment procedures (e.g., advertisements);
  - d. Written information to be provided to subjects;
  - e. Investigator's Brochure (IB) and available safety information;
  - f. Information about payments and compensation available to subjects;
  - g. The investigator's current curriculum vitae and/or other documentation evidencing qualifications; and
  - h. Any other documents that the IRB/IEC may need to fulfil its responsibilities.
3. The IRB should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates that actions were taken;
4. The IRB should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB requests;
5. The IRB should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year;
6. The IRB may request more information than is required by regulation or the ICH-GCP E6 guidance be given to subjects when, in the judgment of the IRB, the additional information would add meaningfully to the protection of the rights, safety, and/or well-being of the subjects;

7. When a nontherapeutic trial is to be carried out with the consent of the subject's LAR, the IRB should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials;
8. Where the protocol indicates that prior consent of the trial subject or the subject's LAR is not possible, the IRB should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e., in emergency situations);
9. The IRB should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject; and
10. The IRB should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

#### **28.7.2 Investigator Responsibilities**

1. The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB, and/or the regulatory authorities;
2. The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information, and in other information sources provided by the sponsor;
3. The investigator should be aware of, and should comply with GCP and applicable regulatory requirements;
4. The investigator should permit monitoring and auditing by the sponsor, and inspection by appropriate regulatory authorities;
5. The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties;
6. The investigator must have adequate resources to conduct the trial, including:
  - a. Being able to demonstrate (e.g., based on retrospective data) the potential for recruiting the required number of subjects within the agreed upon recruitment period;
  - b. Sufficient time to properly conduct and complete the trial within the agreed trial period;

- c. Adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely; and
  - d. Ensuring that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions;
- 7. The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site;
- 8. If the investigator retains the services of any individual or party to perform trial-related duties and functions, the investigator should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated;
- 9. A qualified physician (or dentist, when appropriate), who is an investigator or sub-investigator on the trial, should be responsible for all trial-related medical (or dental) decisions;
- 10. During and following a subject's participation in a trial, the investigator should ensure that adequate medical care is provided for any adverse events, including clinically significant laboratory values, related to the trial. The investigator should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware;
- 11. The investigator should inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and agrees to the primary physician being informed;
- 12. Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights;
- 13. Before initiating a trial, the investigator must have written and dated approval/favorable opinion from the IRB for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects;
- 14. As part of the investigator's application to the IRB, the investigator should provide the IRB with a current copy of the Investigator's Brochure (IB). If the IB is updated during the trial, the investigator should supply a copy of the updated IB to the IRB;
- 15. During the trial the investigator should provide to the IRB all documents subject to review;
- 16. The investigator should sign the protocol, or an alternative contract, to confirm their agreement to comply with the approved protocol;

17. The investigator may not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval from the IRB, except where necessary to eliminate an immediate hazard(s) to trial subjects;
18. In addition to reporting to the IRB, when the investigator implements a deviation from or change in the protocol to eliminate an immediate hazard(s) to subject(s) without prior approval, this must be reported as soon as possible to the sponsor;
19. The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol;
20. The investigator is ultimately responsible for investigational product accountability and for all of the responsibilities for investigational product outlined in section 4.6 of ICH-GCP E6;
21. The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor (and IRB) any premature unblinding;
22. Additional requirements for Informed Consent -
  - a. The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB's approval in advance of use. The subject or the subject's LAR should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented;
  - b. The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's LAR;
  - c. Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's LAR ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's LAR;
  - d. Neither the investigator, nor the trial staff, may coerce or unduly influence a subject to participate or to continue to participate in a trial;
  - e. Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's LAR, and by the person who conducted the informed consent discussion;
  - f. Prior to participation in the trial, the subject or the subject's LAR should receive a copy of the signed and dated written informed consent form and any other

written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's LAR should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects;

- g. If a subject is unable to read or if a LAR is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects is read and explained to the subject or the subject's LAR, and after the subject or the subject's LAR has orally consented to the subject's participation in the trial, and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's LAR and that informed consent was freely given by the subject or the subject's LAR.
- h. Consent for non-therapeutic trials (i.e., a trial in which there is no anticipated direct clinical benefit to the subject) must be obtained from subjects who personally give consent and who sign and date the written informed consent form unless the IRB has expressly approved, in writing, that consent from a LAR is permitted;
- i. The consent discussion and written informed consent form should include the following additional elements:
  - i. An explanation of the trial treatment(s) and the probability for random assignment to each treatment;
  - ii. An explanation of the subject's responsibilities (avoiding any language that appears to restrict subject's rights);
  - iii. An explanation that the monitor(s), auditor(s), the IRB, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or LAR is authorizing such access;
  - iv. An explanation of the anticipated prorated payment, if any, to the subject for participating in the trial;
  - v. An explanation of the reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant;
  - vi. When there is no intended clinical benefit to the subject, the subject should be made aware of this;

- vii. An explanation that, to the extent permitted by applicable laws or regulations, records identifying the subject will not be made publicly available, and, if the results of the trial are published, the subject's identity will remain confidential; and
  - viii. A statement that the trial has the approval of the IRB.
23. Investigators must comply with the requirements for records and reports outlined in section 4.9 and 8 of ICH-GCP E6;
  24. Investigators must comply with the requirements for safety reporting outlined in Section 4.11 of ICH-GCP E6 including the redaction of personally identifying information; and
  25. Investigators must comply with the requirements for premature termination or suspension of a trial outlined in section 4.12 including the requirements for sponsor and IRB reporting.

## **28.8 Transnational Research**

The MaineHealth IRB reviews transnational research involving human subjects to ensure that adequate provisions are in place to protect the rights and welfare of the subjects. All policies and procedures that are applied to research conducted domestically are applied to research in international settings, as appropriate. 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.”*

For federally conducted or supported research, approval of research for foreign institutions or sites “engaged” in research is only permitted if the foreign institution or site holds a FWA 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/EC, 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/EC 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/EC determination, or letter of cooperation, as applicable.

The MaineHealth 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/EC, MaineHealth IRB must receive and review the foreign institution or site's IRB/EC review and approval of each study prior to beginning the research at the foreign institution or site.

In settings where there are no IRBs/ECs, MaineHealth IRB may 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, including other IRBs or committees with experience reviewing research in the region, other MaineHealth investigators with knowledge of the region, or a consultant who is an expert on the region, prior to approval. These individuals may either provide a written review of the research protocol or attend an IRB meeting to provide the MaineHealth IRB with recommendations based on his or her expertise.

### **28.8.1 IRB Responsibilities**

In addition to the IRB review considerations discussed elsewhere in this manual, the IRB will consider the following when reviewing transnational research:

1. The qualifications of the investigator and research staff to conduct research in that country including knowledge of relevant laws, regulations, guidance and custom;
2. Whether the consent process and consent documents are appropriate for the language(s) of the subjects and the subject population, and that arrangements are made to be able to communicate with subjects throughout the study (e.g., to ask and answer questions);
3. How modifications to the research will be handled;
4. How complaints, noncompliance, protocol deviations and unanticipated problems involving risks to subjects or others are handled;
5. How post-approval monitoring will be managed;
6. Whether 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; and
7. Mechanisms for communicating with the investigators and research staff when they are conducting the research in other countries.

### **28.8.2 Investigator Responsibilities**

The investigator conducting transnational research is responsible for:

1. Ensuring that the resources and facilities are appropriate for the nature of the research;
2. Verifying the qualifications of the investigators and research staff for conducting research in the country(ies);

3. Obtaining all appropriate host country permissions to conduct research (e.g., institutional, governmental or ministerial, IRB, local, or tribal);
4. Complying with the requirements of country law (specified in the country-specific AAHRPP Addenda to the Evaluation Instrument); including, when applicable, requirements for research involving investigational articles;
5. Ensuring that the consent process and consent document are appropriate for the language(s) of the subjects and the subject population, and that arrangements are made to be able to communicate with subjects throughout the study (e.g., to ask and answer questions);
6. Ensuring that the following activities will occur:
7. Initial review, continuing review, and review of modifications;
8. Post-approval monitoring of the conduct of the research in accordance with the plan approved by the IRB; and
9. Handling of complaints, noncompliance and unanticipated problems involving risk to subjects or others;
10. Not relying upon an IRB or EC that does not have policies and procedures for the activities listed above;
11. Ensuring that reportable information such as complaints, noncompliance, protocol deviations and unanticipated problems involving risks to participants or other are communicated to the IRB;
12. Notifying 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.); and
13. Ensuring that there are mechanisms for communicating with the IRB when they are conducting the research in other countries.

### **28.8.3 Consent Documents**

The informed consent documents must be appropriate for and in a language understandable to the proposed subjects. The IRB will review the proposed document per section 15.8.1.

### **28.8.4 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 are both involved in the review of research, there is a plan for coordination and communication with the local IRB/ECs.

The IRB requires documentation of regular correspondence between the MaineHealth investigator and the foreign institution or site and may require verification from sources other

than the MaineHealth investigator that there have been no changes made to the research since its last review.

## **28.9 Community Based Research**

Community based research (CBR) is research that is based in a community and conducted in collaboration with members of that community. *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 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 the investigator and community partners that describes how they will work together?