



Human Research Protection Program / Institutional Review Board
Standard Operating Procedure
2018 Common Rule

**For Studies Initially Approved on
or After January 21, 2019**

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1 Special Topics

1.1 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.

1.2 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.

1.2.1 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.

1.2.2 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.

1.2.3 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.

1.2.4 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.

1.2.5 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.

1.2.6 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.

1.3 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.

1.3.1 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.

1.3.2 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.

1.3.3 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.

1.4 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 to 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).

1.4.1 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.

1.5 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

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)
- **Institutional Certification** from Grants and Contracts (template available here: 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/>.

1.6 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.

1.6.1 Key DoD Standards and Requirements

1.6.1.1 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).

1.6.1.2 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.

1.6.1.3 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.

1.6.1.4 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.

1.6.1.5 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.

1.6.1.6 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.

1.6.1.7 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.

1.6.1.8 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.

1.6.1.9 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.

1.6.1.10 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.

1.6.1.11 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.

1.7 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).

1.7.1 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.

1.7.2 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.

1.8 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.

1.8.1 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.

1.8.2 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.

1.8.3 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.

1.8.4 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.

1.9 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?