



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 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

1.1 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 **unless the reviewer determines that the research involves 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
- **Research for which limited IRB review is a condition of exemption under 45 CFR 46.104(d)(2)(iii) and (d)(3)(i)(C)**

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.

1.1.1 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).

1.1.2 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 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.)

1.1.3 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.

1.1.4 Expedited Review Procedures

Under an expedited review procedure, IRB review of new studies is carried out by the IRB Chair or designated reviewer, 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. If review is conducted by a designated reviewer, that individual must be professionally competent (i.e., experienced with, and having demonstrated the ability to apply, IRB review requirements and with appropriate scientific or scholarly expertise) to conduct expedited review.

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 (See section 12.2.4). 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. **When a reviewer determines that research subject to the Common Rule falls within the expedited categories but involves more than minimal risk, the reviewer will document the rationale for that determination in the checklist and refer the research for review by the convened IRB.** If the research **otherwise** does not meet the criteria for expedited review, 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.

1.1.5 Informing the IRB

Members of the IRB will be apprised of expedited review approvals, **including limited IRB reviews conducted using expedited review procedures**, 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.

1.2 Convened IRB Meetings

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

1.2.1 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). Special meetings may be called as needed by the Chair, IRB Manager, or ORC Director.

1.2.2 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.

1.2.3 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.

1.2.4 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.)
- Initial Submission **Supplemental** Form
- 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.

1.2.5 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 subjects vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity or economically or educationally disadvantaged persons, 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.

1.2.6 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.

1.2.7 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.

1.3 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 subjects vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.
4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 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.

1.3.1 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.

1.3.1.1 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. MMCR 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.

1.3.2 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 subjects vulnerable to coercion or undue influence such as children, prisoners, individuals with impaired decision-making capacity, 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.

1.3.2.1 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.

1.3.3 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.

1.3.4 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.

1.3.5 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**.

1.3.5.1 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.

1.3.5.2 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"

1.3.5.3 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](#).

1.3.6 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.

1.4 Additional Considerations

1.4.1 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.

1.4.2 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. **For research subject to the 2018 Common Rule, the IRB will conduct continuing review of**

research requiring review by the convened IRB at intervals appropriate to the degree of risk of the research, but not less than once per year, except as described in Section 12.5;

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.

1.4.3 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 **unless the study does not require continuing review**. If an approval period of less than one year is specified by the IRB **for research that is subject to continuing review**, the reason for more frequent review must be documented in the minutes or the expedited reviewer's checklist.

1.4.4 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 **since previous IRB review**.

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:

1. The nature, probability, and magnitude of anticipated risks to subjects;
2. The degree of uncertainty regarding the risks involved;
3. Whether the research involves novel therapies or procedures;
4. The vulnerability(ies) of the subject population;
5. The projected rate of enrollment;
6. The experience and expertise of the investigators;
7. The IRB's previous experience with the investigators or the sponsor (e.g., compliance history, complaints from subjects, etc.);
8. The probable nature and frequency of changes that may ordinarily be expected in the type of research;
9. Whether the research undergoes routine independent monitoring;
10. 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; and
11. Any other factors that suggest independent verification is warranted.

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).

1.4.5 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.

1.4.6 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.

1.4.7 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).

1.4.8 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).

1.4.9 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.

1.4.10 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.

1.4.11 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.

1.4.12 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.

1.5 Continuing Review

(For studies receiving initial approval on or before 1/20/19, please refer to SOP's available at www.mmcri.org for content of this section).

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

Unless an IRB determines otherwise, continuing review of research subject to the 2018 Common Rule (the revised Common Rule) is not required in the following circumstances:

- Research eligible for expedited review in accordance with 45 CFR 46.110;
- Research reviewed by the IRB in accordance with the limited IRB review described elsewhere in these SOPs;
- Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:
 - Data analysis, including analysis of identifiable private information or identifiable biospecimens, or

- Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

Studies that fall into these categories and are determined by the IRB to not require continuing review are still subject to prompt reporting requirements(e.g., proposed amendments, unanticipated problems involving risk to subjects or others, protocol deviation/violations/non-compliance). **They will also require submission of an annual progress report** that will collect information regarding status of the research activity. Investigators will receive courtesy reminder e-mail notices for completion of the progress report. ORC staff will review the report for compliance with institutional policies (verification of human subjects training, COI review, etc). Failure to submit an annual progress report as required will constitute non-compliance with MaineHealth's HRPP policy and may result in suspension of the study until compliance with this policy is confirmed.

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

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

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

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

1.5.1 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

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.

1.5.2 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.

1.5.3 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.

1.5.4 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. **If the research subject to the 2018 Common rule (the revised Common Rule) no longer requires continuing review (See Section 12.5) and the IRB reviewer determines that continuing review is required, the reviewer shall document the rationale in the checklist.**

Generally, if research did not qualify for expedited review at the time of initial review, it does not qualify for expedited review at the time of continuing review, **unless it was approved under the 2018 Common Rule, and has progressed to the point that it involves only one or both of the following:**

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

Or, the study was approved under the pre-2018 Common Rule, and qualifies is 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.

1.5.5 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).

1.5.6 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.

1.5.6.1 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.

1.6 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.

1.6.1 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.

1.6.2 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.

1.6.3 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.

1.6.4 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).

1.6.5 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.

1.7 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.