Investigator Manual[i]
for Human Subjects Research

HRP-103 | 5/14/2026 | Responsible Office: IRB

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Scope

Throughout this document “institution” refers to University of Texas Health Science Center at San Antonio.

What is the purpose of this manual?

This document, HRP-103 - INVESTIGATOR MANUAL, is designed to guide you through policies and procedures related to the conduct of Human Research that are specific to this institution.

General information regarding Human Research protections and relevant federal regulations and guidance is incorporated into the required human protections training. For additional information see below: “What training do my staff and I need in order to conduct Human Research?”

What is Human Research?

HRP-101 - HUMAN RESEARCH PROTECTION PROGRAM PLAN defines the activities that this institution considers to be “Human Research.” An algorithm for determining whether an activity is Human Research can be found in HRP-310 - WORKSHEET - *Human Research Determination*, located in the ERMS library. Use this document for guidance as to whether an activity meets either the DHHS or FDA definition of Human Research, keeping in mind that the IRB makes the ultimate determination in questionable cases as to whether an activity constitutes Human Research subject to IRB oversight.

You are responsible not to conduct Human Research without prior IRB review and approval (or an institutional review and determination of exempt Human Research). If you have questions about whether an activity is Human Research, contact the IRB Office who will provide you with a determination. If you wish to have a written determination, provide a written request to the IRB Office.

What is the Human Research Protection Program?

HRP-101 - HUMAN RESEARCH PROTECTION PROGRAM PLAN describes this institution’s overall plan to protect subjects in Human Research, and includes the following:

- The mission of the Human Research Protection Program.
- The ethical principles that the institution follows governing the conduct of Human Research.
- The applicable laws that govern Human Research.
- When the institution becomes “engaged in Human Research” and when someone is acting as an agent of the institution conducting Human Research.
- The types of Human Research that may not be conducted.
- The roles and responsibilities of individuals within the institution.

What training do my staff and I need to conduct Human Research?

This section describes the training requirements imposed by the IRB. You may have additional training imposed by other federal, state, or institutional policies.

All members of the research team involved in the design, conduct, or reporting of the research must complete training. Members of the research team who have not completed human research protections training may not take part in aspects of the research that involve human subjects. In addition, all members of the research team conducting a NIH funded clinical trial must complete Good Clinical Practice (GCP) training. Research team members who do not meet required training requirements will not be approved.

Human subjects and GCP training must be completed using the Collaborative Institutional Training Initiative (CITI) human subjects online training program.

The CITI site can be accessed at http://www.citiprogram.org/.

Additional training for International Air Transport Association (IATA), Participant Payment, Velos, and Conflict of Interest (COI) should be accessed via UT Health Learns.

CITI training is valid for a three-year period, after which time the training must be repeated. Research team members are required to comply with all automated training expiration reminders issued by CITI and UT Health Learns.

What financial interests do my staff and I need to disclose when conducting Human Research?

Individuals involved in the design, conduct, or reporting of research, research consultation, teaching, professional practice, institutional committee memberships, and service on panels such as Institutional Review Boards or Data and Safety Monitoring Boards are considered to have an institutional responsibility.

All individuals involved in the design, conduct, or reporting of research are required to disclose financial interests in the New Study SmartForm in the electronic IRB system:

- On submission of an initial review.
- At least annually as part of continuing review.
- Within 30 days of discovering or acquiring (e.g., through purchase, marriage, or inheritance) a new financial interest.

Individuals with reimbursed or sponsored travel by an entity other than a federal, state, or local government agency, higher education institution or affiliated research institute, academic teaching hospital, or medical center are required to disclose the purpose of the trip, the identity of the sponsor or organizer, the destination, and the duration of the travel.

Individuals subject to this policy are required to complete financial conflicts of interest training initially, at least every four years, and immediately when:

- Joining the institution.

- Financial conflicts policies are revised in a manner that changes investigator requirements.
- Non-compliant with financial conflicts policies and procedures.

Additional details can be found in HRP-055 - POLCY - *Financial Conflicts of Interest*.

How do I submit new Human Research to the IRB?

All IRB submissions must include a protocol. When applicable, the submission must also include:

- Written materials that will be provided to or meant to be seen or heard by subjects including (but not limited to) evaluation instructions and surveys, recruitment materials, and consent documents.
- Details pertaining to study funding, research locations, and participating (external) sites.
- Study staff information, including any Conflicting Interests that are Related to the Research.
- Information related to drugs, biologics, supplements, food and/or devices that are under study.

To submit to the IRB, complete the New Study SmartForm in the electronic IRB system, attach all requested supplements. Once completed, submit the SmartForm by having the PI by click the “Submit” activity. Maintain electronic copies of all information submitted to the IRB in case revisions are required.

How do I submit a request to use a Humanitarian Use Device (HUD) for clinical use?

This Institution utilizes the IRB to review and approve the use of a HUD before it can be used at a facility for clinical care. You can refer to HRP-323 - WORKSHEET - *Criteria for Approval HUD* for additional information regarding the criteria that the IRB uses to review and approve HUD uses. The clinical use of a HUD is not considered Human Research but must still be submitted for review and approval by the IRB prior to clinical use (with the exception of emergency use). An informed consent form is not required by the IRB for HUD use.

Complete the New Study SmartForm in the electronic IRB system, attach all requested supplements, and have the SmartForm submitted by the PI by clicking the “Submit” activity. Maintain electronic copies of all information submitted to the IRB in case revisions are required. Before submitting the research for initial review, you must:

- Obtain the financial interest status (“yes” or “no”) of each research staff.
- Obtain the agreement of research staff to his/her role in the research.

How do I request to rely on an external IRB?

Complete the New Study SmartForm in the electronic IRB system, indicate that an External IRB will serve as the IRB of Record and attach all requested supplements. Have the SmartForm submitted by the PI by clicking the "Submit" activity. Maintain electronic copies of all information submitted to the IRB in case revisions are required.

How do I request that this IRB serve as the single IRB of record (sIRB) for my collaborative or multi-site research study?

On the New Study SmartForm in the electronic IRB system, indicate if the study is a multi-site or collaborative research study, then select "Yes" to the question "Will your IRB act as the single IRB of record for other participating sites?" Complete the rest of the New Study SmartForm and attach all available supplements. Participating sites are added by executing the "Add Participating Site" activity. Have the SmartForm submitted by the PI by clicking the "Submit" activity.

How do I write an Investigator Protocol?

Use HRP-503 - TEMPLATE PROTOCOL as a starting point for drafting a new Investigator Protocol and reference the instructions in italic text for the information the IRB looks for when reviewing research. Here are some key points to remember when developing an Investigator Protocol:

- Blue italics in HRP-503 - TEMPLATE PROTOCOL serve as guidance to investigators when developing an Investigator Protocol for submission to the IRB. All italicized comments are meant to be deleted prior to submission.
- For any items described in the sponsor's protocol or other documents submitted with the application, investigators may simply reference the page numbers of these documents within the Investigator Protocol rather than repeat information.
- When writing an Investigator Protocol, always keep an electronic copy. You will need to modify this copy when making changes to the Investigator Protocol.
- If you believe your activity may not be Human Research, contact the IRB Office prior to developing your Investigator Protocol.
- Note that, depending on the nature of your research, certain sections of the template may not be applicable to your Investigator Protocol. Indicate this as appropriate.
- You may not involve any individuals who are members of the following populations as subjects in your research unless you indicate this in your inclusion criteria, as the inclusion of subjects in these populations has regulatory implications.
    - Adults unable to provide legally effective consent
    - Individuals who are not yet adults (infants, children, teenagers)
    - Pregnant women

    - Prisoners
- This institution notes that employees under the supervision of any investigator are considered and evaluated by the IRB as possible individuals with diminished autonomy and/or vulnerable to undue influence.
- If you are conducting community-based participatory research, you may contact the IRB Office for information about:
    - Research studies using a community-based participatory research design
    - Use of community advisory boards
    - Use of participant advocates
    - Partnerships with community-based institutions or organizations

How do I create a consent document?

Use HRP-502 - TEMPLATE CONSENT DOCUMENT to create a consent document.

Note that all long form consent documents and all summaries for short form consent documents must contain all of the required and all additional appropriate elements of informed consent disclosure. Review the "Long Form of Consent Documentation" section in HRP-314a - WORKSHEET - *Criteria for Consent*, to ensure that these elements are addressed. When using the short form of consent documentation, the appropriate signature block from HRP-502 - TEMPLATE CONSENT DOCUMENT should be used on the short form.

If your research study meets the requirements for an exemption and there are interactions with subjects, you may use an abbreviated process for obtaining consent. Consent can be verbal, but you must provide the following information to participants through an information sheet or written script:

- The subject is being asked to participate in a research study;
- A description of the procedure(s) the participant will be asked to complete;
- Participation is voluntary; and
- The investigator's name and contact information.

We recommend that you date the revisions of your consent documents to ensure that you use the most recent version approved by the IRB.

Do I need to obtain informed consent in order to screen, recruit, or determine the eligibility of prospective subjects?

The IRB may approve a research proposal in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without the informed consent of the prospective subject or the subject's legally authorized representative, if either of the following conditions are met:

> (1) The investigator will obtain information through oral or written communication with the prospective subject or legally authorized representative, OR

(2) The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

The research protocol should include information about how potential subjects will be identified and recruited in order for the IRB to be able to determine whether informed consent for these activities is required.

Contact the IRB Office with additional questions or for further guidance regarding the requirement to obtain HIPAA authorization or a waiver to obtain HIPAA authorization for recruitment purposes.

What are the different regulatory classifications that research activities may fall under?

Submitted activities may fall under one of the following four regulatory classifications:

- Not "Human Research": Activities must meet the institutional definition of "Human Research" to fall under IRB oversight. Activities that do not meet this definition are not subject to IRB oversight or review. Review the IRB Office's HRP-310 - WORKSHEET - *Human Research Determination* for reference. Contact the IRB Office in cases where it is unclear whether an activity is Human Research.
- Exempt: Certain categories of Human Research may be exempt from regulation but require IRB review. It is the responsibility of the institution, not the investigator, to determine whether Human Research is exempt from IRB review. Review the IRB Office's HRP-312 - WORKSHEET - *Exemption Determination* for reference on the categories of research that may be exempt.
- Review Using the Expedited Procedure: Certain categories of non-exempt Human Research may qualify for review using the expedited procedure, meaning that the project may be approved by a single designated IRB reviewer, rather than the convened board. Review the IRB Administration's HRP-313 - WORKSHEET - *Expedited Review* for reference on the categories of research that may be reviewed using the expedited procedure.
- Review by the Convened IRB: Non-Exempt Human Research that does not qualify for review using the expedited procedure must be reviewed by the convened IRB.

What are the decisions the IRB can make when reviewing proposed research?

The IRB may approve research, require modifications to the research to secure approval, table research, defer research, or disapprove research:

- Approval: Made when all criteria for approval are met. See "How does the IRB decide whether to approve Human Research?" below.

- Modifications Required to Secure Approval: Made when IRB members require specific modifications to the research before approval can be finalized.
- Tabled: Made when the IRB cannot approve the research at a meeting for reasons unrelated to the research, such as loss of quorum. When taking this action, the IRB automatically schedules the research for review at the next meeting.
- Deferred: Made when the IRB determines that the board is unable to approve research and the IRB suggests modifications that might make the research approvable. When making this motion, the IRB describes its reasons for this decision, describes modifications that might make the research approvable, and gives the investigator an opportunity to respond to the IRB in person or in writing.
- Disapproval: Made when the IRB determines that it is unable to approve research and the IRB cannot describe modifications that might make the research approvable. When making this motion, the IRB describes its reasons for this decision and gives the investigator an opportunity to respond to the IRB in person or in writing.

How does the IRB decide whether to approve Human Research?

The criteria for IRB approval can be found in HRP-312 - WORKSHEET - *Exemption Determination* for exempt Human Research and HRP-314 - WORKSHEET - *Criteria for Approval* for non-exempt Human Research. The latter worksheet references other checklists that might be relevant. All checklists and worksheets can be found on the IRB Web site.

These checklists are used for initial review, continuing review, and review of modifications to previously approved Human Research.

You are encouraged to use the checklists to write your Investigator Protocol in a way that addresses the criteria for approval.

What will happen after IRB review?

The IRB will provide you with a written decision indicating that the IRB has approved the Human Research, requires modifications to secure approval, or has disapproved the Human Research.

- If the IRB has approved the Human Research: The Human Research may commence once all other institutional approvals have been met. IRB approval is usually good for a limited period of time which is noted in the approval letter.
- If the IRB requires modifications to secure approval and you accept the modifications: Make the requested modifications and submit them to the IRB. If all requested modifications are made, the IRB will issue a final approval. Research cannot commence until this final approval, and any other institutional approvals, are received. If you do not accept the modifications, write up your response and submit it to the IRB.
- If the IRB defers the Human Research: The IRB will provide a statement of the reasons for deferral and suggestions to make the study approvable and give you an opportunity

to respond in writing. In most cases if the IRB's reasons for the deferral are addressed in a modification, the Human Research can be approved.

- If the IRB disapproves the Human Research: The IRB will provide a statement of the reasons for disapproval and give you an opportunity to respond in writing.

In all cases, you have the right to address your concerns to the IRB directly at an IRB meeting.

What are my obligations after IRB approval?

1) Do not start Human Research activities until you have the final IRB approval letter.
2) Do not start Human Research activities until you have obtained all other required institutional approvals, including approvals of departments or divisions that require approval prior to commencing research that involves their resources.
3) Ensure that there are adequate resources to carry out the research safely. This includes, but is not limited to, sufficient investigator time, appropriately qualified research team members, equipment, and space.
4) Ensure that Research Staff are qualified (e.g., including, but not limited to, appropriate training, education, expertise, credentials, protocol requirements and, when relevant, privileges) to perform procedures and duties assigned to them during the study.
5) Update the IRB office with any changes to the list of study personnel.
6) Personally conduct or supervise the Human Research. Recognize that the investigator is accountable for the failures of any study team member.
   a) Conduct the Human Research in accordance with the relevant current protocol as approved by the IRB, and in accordance with applicable federal regulations and local laws.
   b) When required by the IRB, ensure that consent or permission is obtained in accordance with the relevant current protocol as approved by the IRB.
   c) Do not modify the Human Research without prior IRB review and approval unless necessary to eliminate apparent immediate hazards to subjects.
   d) Protect the rights, safety, and welfare of subjects involved in the research.
7) Submit to the IRB:
   a) Proposed modifications as described in this manual. (See "How do I submit a modification?")
      i) Single subject protocol exceptions should be submitted via the Report New Information (RNI) process.
   b) A continuing review application as requested in the approval letter. (See "How do I submit continuing review?")
   c) A continuing review application when the Human Research is closed. (See "How Do I Close Out a Study?")
8) Complete the Report New Information SmartForm within five business days of becoming aware of the following items:
   a) Information that indicates a new or increased risk, or a new safety issue. For example:
      i) New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor report, or investigator finding) indicates an increase in the frequency or magnitude of a previously known risk or uncovers a new risk.

ii) An investigator brochure, package insert, or device labeling is revised to indicate an increase in the frequency or magnitude of a previously known risk, or describe a new risk.
iii) Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a research protocol.
iv) Protocol violation that harmed subjects or others or that indicates subjects or others might be at increased risk of harm.
v) Complaint of a subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm.
vi) Any changes significantly affecting the conduct of the research.

b) Harm experienced by a subject or other individual, which in the opinion of the investigator are **unexpected** and **probably related** to the research procedures.
i) A harm is "unexpected" when its specificity or severity are inconsistent with risk information previously reviewed and approved by the IRB in terms of nature, severity, frequency, and characteristics of the study population.
ii) A harm is "probably related" to the research procedures if, in the opinion of the investigator, the research procedures more likely than not caused the harm.

c) Non-compliance with the federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance.
d) Audit, inspection, or inquiry by a federal agency and any resulting reports (e.g., FDA Form 483).
e) Written reports of study monitors.
f) Failure to follow the protocol due to the action or inaction of the investigator or research staff.
g) Breach of confidentiality.
h) Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject.
i) Incarceration of a subject in a study not approved by the IRB to involve prisoners.
j) Complaint of a subject that cannot be resolved by the research team.
k) Premature suspension or termination of the protocol by the sponsor, investigator, or institution.
l) Unanticipated adverse device effect (any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects).

9) Submit an updated disclosure of financial interests within thirty days of discovering or acquiring (e.g., through purchase, marriage, or inheritance) a new financial interest.
10) Do not accept or provide payments to professionals in exchange for referrals of potential subjects ("finder's fees").
11) Do not accept payments designed to accelerate recruitment that were tied to the rate or timing of enrollment ("bonus payments").

12) See additional requirements of various federal agencies in Appendix A. These represent additional requirements and do no override the baseline requirements of this section.
13) If the study is a clinical trial and supported by a Common Rule agency, one IRB-approved version of a consent form that has been used to enroll participants must be posted on a public federal website designated for posting such consent forms. The form must be posted after recruitment closes, and no later than 60 days after the last study visit. Please contact the study sponsor with any questions.
    a) If certain information should not be made publicly available on a Federal website (e.g., confidential commercial information), the supporting Federal department or agency may permit or require redactions to the information posted. Contact the Federal department or agency supporting the clinical trial for a formal determination.
    b) Contact the supporting Federal department or agency sponsor with any other questions regarding consent form posting obligations.

What are my obligations as the overall study PI for a sIRB study?

1) Coordinate with HRPP personnel to determine whether this institution's IRB can act as the single IRB for all or some institutions participating in the study or if an external IRB will assume oversight.
2) Identify all sites that will be engaged in the human research and require oversight by the IRB.
3) Ensure that all sites receive a request to rely on the reviewing IRB and that all institutional requirements are satisfied before a study is activated at a relying site.
4) Collaborate with the reviewing IRB to document roles and responsibilities for communicating and coordinating key information from study teams and the IRB or HRPP at relying sites.
5) Respond to questions or information requests from study teams or the IRB or HRPP staff at relying sites.
6) Provide relying site investigators with the policies of the reviewing IRB.
7) Provide relying site investigators with the IRB-approved versions of all study documents.
8) Help prepare and submit IRB applications on behalf of all sites. This includes initial review, modifications, personnel updates, reportable new information and continuing review information for all sites.
9) Establish a process for obtaining and collating information from all sites and submitting this information to the reviewing IRB. This includes site-specific variations in study conduct, such as the local consent process and language, subject identification and recruitment processes and local variations in study conduct.
10) Ensure that consent forms used by relying sites follow the consent template approved by the reviewing IRB and include required language as specified by the relying sites.
11) Provide site investigators with all determinations and communications from the reviewing IRB.
12) Submit reportable new information from relying sites to the reviewing IRB in accordance with the terms outlined in the authorization agreement or communication plan.
13) Report the absence of continuing review information from relying sites if they do not provide the required information prior to submission of the continuing review materials to the

reviewing IRB. Notifying the relying site of their lapse in approval and applicable corrective actions.
14) Provide study records to the relying institution, reviewing IRB or regulatory agencies upon request.

What are my obligations as investigator when relying on an external IRB?

1) Obtain appropriate approvals from this institution prior to seeking review by another IRB.
2) Comply with determinations and requirements of the reviewing IRB.
3) Provide the reviewing IRB with requested information about local requirements or local research context issues relevant to the IRB's determination prior to IRB review.
4) Notify the reviewing IRB when local policies that impact IRB review are updated.
5) Cooperate in the reviewing IRB's responsibility for initial and continuing review, record keeping and reporting, and provide all information requested by the reviewing IRB in a timely manner.
6) Disclose conflicts of interest as required by the reviewing IRB and comply with management plans that may result.
7) Promptly report to the reviewing IRB any proposed changes to the research and do not implement those changes to the research without prior IRB review and approval, except where necessary to eliminate apparent immediate hazards to the participants.
8) When enrolling participants, obtain, document and maintain records of consent for each participant or each participant's legally authorized representative.
9) Promptly report to the reviewing IRB any unanticipated problems involving risks to participants or others according to the requirements specified in the reliance agreement.
10) Provide the reviewing IRB with data safety monitoring reports in accordance with the reviewing IRB's reporting policy.
11) Report non-compliance, participant complaints, protocol deviations or other events according to the requirements specified in the reliance agreement.
12) Specify the contact person and provide contact information for researchers and research staff to obtain answers to questions, express concerns, and convey suggestions regarding the use of the reviewing IRB.
13) Report to the local IRB any changes to the study required by this institution. Report updates to the overall study using the "Update Study Details" activity. Report modifications to this site (e.g., personnel changes) using the "Create Site Modification" activity.

How do I document consent?

Use the signature block approved by the IRB. Complete all items in the signature block, including dates and applicable checklists.

The following are the requirements for long form consent documents:

- The subject or representative signs and dates the consent document.
- The individual obtaining consent signs and dates the consent document.

- Whenever the IRB or the sponsor require a witness to the oral presentation, the witness signs and dates the consent document.
- For subjects who cannot read, and whenever required by the IRB or the sponsor, a witness to the oral presentation signs and dates the consent document.
- A copy of the signed and dated consent document is to be provided to the subject.

The following are the requirements for short form consent documents:

- The subject or representative signs and dates the short form consent document.
- The individual obtaining consent signs and dates the summary.
- The witness to the oral presentation signs and dates the short form consent document and the summary.
- Copies of the signed and dated consent document and summary are provided to the subject/representative.
- Obtain a translated copy of the IRB-approved English version of the long form consent promptly and submit to the IRB for review.
    - After IRB approval of the translated version, provide it to the subject or LAR as soon as possible.

How do I submit a modification?

Complete the Modification SmartForm in the electronic IRB system, attach all requested supplements, and have the SmartForm submitted by the PI by clicking the “Submit” activity. Maintain electronic copies of all information submitted to the IRB in case revisions are required. Please note that research must continue to be conducted without inclusion of the modification until IRB approval is received.

How do I submit continuing review?

Complete the Continuing Review SmartForm in the electronic IRB system, attach all requested supplements, and have the SmartForm submitted by the PI by clicking the “Submit” activity. Maintain electronic copies of all information submitted to the IRB in case revisions are required.

If the continuing review involves modifications to previously approved research, submit those modifications either as a combined Modification and Continuing Review or as a separate request for modification using the Modification SmartForm the electronic system.

If the continuing review application is not received by the date requested in the approval letter, you will be restricted from submitting new Human Research until the completed application has been received.

If the approval of Human Research expires, all Human Research procedures related to the protocol under review must cease, including recruitment, advertisement, screening, enrollment, consent, interventions, interactions, and collection or analysis of private identifiable information. Continuing Human Research procedures is a violation of institutional policy. If current subjects will be harmed by stopping Human Research procedures that are available outside the Human

Research context, provide these on a clinical basis as needed to protect current subjects. If current subjects will be harmed by stopping Human Research procedures that are not available outside the Human Research context, immediately contact the IRB Director and provide a written list of the currently enrolled subjects and why they will be harmed by stopping Human Research procedures.

How do I close out a study?

Complete the Continuing Review SmartForm in the electronic IRB system, attach all requested supplements, and have the SmartForm submitted by the PI by clicking the “Submit” activity. Maintain electronic copies of all information submitted to the IRB in case revisions are required. If you fail to submit a continuing review form to close out Human Research, and your approval expires, you may be restricted from submitting new Human Research until the completed application has been received.

In cases where the participating site is closing but the study remains open, submit a modification for the participating site application. Complete the Modification SmartForm in the electronic IRB system indicating the request for closure of the site and have the PI select the “Submit” activity.

How long do I keep records?

Maintain your Human Research records, including signed and dated consent documents for at least three years after completion of the research. Maintain signed and dated HIPAA authorizations and consent documents that include HIPAA authorizations for at least six years after completion of the research.

If your Human Research is sponsored, contact the sponsor before disposing of Human Research records.

In cases where the participating site requires a longer retention period for Human Research records and HIPAA authorizations, you should defer to the participating site policies.

What if I need to use an unapproved drug, biologic, or device and there is no time for IRB review?

Contact the IRB Office or IRB chair immediately to discuss the situation. If there is no time to make this contact, see HRP-322 - WORKSHEET - *Emergency Use* for the regulatory criteria allowing such a use and make sure these are followed. Use HRP-502 - TEMPLATE CONSENT DOCUMENT - *Emergency or Compassionate Device Use* to prepare your consent document. You will need to submit a report of the use to the IRB within five working days of the use and for drugs and biologics, submit an IRB application for initial review within 30 days.

If you fail to submit the report within five working days or the IRB application for initial review within 30 days, you may be restricted from submitting new Human Research until the report and IRB application for initial review have been received.

Emergency use of an unapproved drug or biologic in a life-threatening situation without prior IRB review is "research" as defined by FDA, and the individual getting the test article is a "subject" as defined by FDA. Emergency use is therefore governed by FDA regulations for IRB review and informed consent. Emergency use of an unapproved device without prior IRB review is not "research" as defined by FDA, and the individual getting the test article is not a "subject" as defined by FDA. However, FDA guidance recommends following similar rules as for emergency use of an unapproved drug or biologic.

Individuals getting an unapproved drug, biologic, or device without prior IRB review are not considered "subjects" as defined by DHHS, and their results cannot be included in prospective "research" as defined by DHHS.

How do I submit a non-emergency expanded access request for an unapproved drug, biologic, or device to the IRB?

There are five different types of non-emergency use expanded access:

1. Individual patient expanded access use of an investigational drug

Individual patient drug expanded access requests should be submitted to the IRB as a new study. If the study team checked "Request for Authorization to Use Alternative IRB Review Procedures" on FDA Form 3926 (field 10.b.) or has a separate waiver request included with FDA Form 1571 for the purpose of obtaining concurrence from an IRB Chair or designee, this information should be included in the application. Instead of uploading a protocol, the submission should include the following:

- A thorough patient history and treatment plan, included in the Form FDA 3926 or in a separate document that includes:
    - The proposed daily dose, route, and frequency of administration of planned treatment; duration of planned treatment; criteria for discontinuation of treatment; and planned dose modifications for adverse events;
    - The planned monitoring for adverse events, response to treatment, and changes in clinical status, as well as proposed modifications to the treatment plan to mitigate risks to the patient if appropriate;
    - The key details of the patient's history, including diagnosis and summary of prior therapy (including response to such therapy); the reason for request, including an explanation of why the patient lacks other therapeutic options; and information regarding a patient's relevant clinical characteristics (such as comorbid conditions and concomitant medications) that is necessary to assess the potential for increased risks of the drug; and
    - - A summary of known risks of the drug

Use HRP-503n - Template - *Consent Form for Treatment* to prepare your consent document. A Continuing Review application must be submitted to the IRB at least annually, and any modifications or new information should be reported accordingly.

2. Compassionate Use (Individual patient/small group access) of a device

Requests for compassionate use of a device should be submitted to the IRB as a new study. See HRP-325 - WORKSHEET – Device Compassionate Use for the regulatory criteria allowing such a use and make sure these are followed. The FDA does not consider the compassionate use of an unapproved device to be a clinical investigation, however it is expected that informed consent be obtained. Use H HRP-503n - Template - *Consent Form for Treatment* to prepare your consent document.

Instead of uploading a protocol, the submission should include a summary of the conditions constituting the compassionate use, other relevant details of the case, approval from the device manufacturer, device/product manual, FDA authorization, and any other relevant information (i.e., patient-facing materials, etc..). Continuing review is not required for compassionate use, however if any problems occurred as a result of device use, these should be discussed in the follow-up report and reported to the IRB as soon as possible.

3. Intermediate-size patient population access of a drug
4. Expanded access for widespread use of a drug
5. Treatment use of a device

Requests for any of these three (3) types of expanded access use should be submitted to the IRB as a new study. Submissions should include the protocol, consent form, and other pertinent information (i.e., Investigator's Brochure, device/product manual, patient-facing materials, etc..). Use HRP-502 – TEMPLATE CONSENT DOCUMENT to prepare your consent document. A Continuing Review application must be submitted to the IRB at least annually, and any modifications or new information should be reported accordingly.

How do I transfer responsibility to a new principal investigator?

Changes of PI often prompt changes to other parts of the study. Review all consent/assent forms, recruitment materials and other documents to make certain they have been updated to reflect the change. The current PI may transfer responsibility to a new PI by submitting a modification (See "How do I submit a modification?").

If the current PI is leaving the institution but will remain a study team member, please contact the IRB Office to determine if a reliance agreement is appropriate.

If the current PI is leaving the institution and plans to take research data or specimens with them, there are contractual agreements that may be needed in order to share individual level human subjects research data/specimens.

If a PI goes on an unanticipated leave or there is an abrupt departure from the institution, a modification should be submitted by a current member of the study team as soon as possible to update the PI. If a modification is not going to be submitted, Complete the Reportable New Information SmartForm in the electronic IRB system. The submission should include an explanation as to why a modification will not be submitted, whether the unanticipated leave is temporary (and for how long) or permanent, and who will be responsible for the conduct of the study during this time.

How do I get additional information and answers to questions?

This document and the policies and procedures for the Human Research Protection Program are available in the ERMS-IRB Library.

If you have any questions or concerns about the Human Research Protection Program, contact the IRB Office at:

Office of the Institutional Review Board
8403 Floyd Curl Drive, Mail Code 7830
San Antonio, TX 78229
Email: irb@uthscsa.edu
210-567-8250
Website: https://uthscsa.edu/research/about/directory/irb/

If you have questions, concerns, complaints, allegations of undue influence, allegations or findings of non-compliance, or input regarding the Human Research Protection Program that cannot be addressed by contacting the IRB Office, follow the directions in HRP-101 - HUMAN RESEARCH PROTECTION PROGRAM PLAN under “Reporting and Management of Concerns.”

Appendix A-1 *Additional Requirements for DHHS-Regulated Research*[ii]

1. When a subject decides to withdraw from a clinical trial, the investigator conducting the clinical trial should ask the subject to clarify whether the subject wishes to withdraw from all components of the trial or only from the primary interventional component of the trial. If the latter, research activities involving other components of the clinical trial, such as follow-up data collection activities for which the subject previously gave consent may continue. The investigator should explain to the subject who wishes to withdraw the importance of obtaining follow-up safety data about the subject.
2. Investigators are allowed to retain and analyze already collected data relating to any subject who chooses to withdraw from a research study or whose participation is terminated by an investigator without regard to the subject's consent, provided such analysis falls within the scope of the analysis described in the IRB-approved protocol. This is the case even if the data include identifiable private information about the subject.
3. For research not subject to regulation and review by FDA, investigators, in consultation with the funding agency, can choose to honor a research subject's request that the investigator destroy the subject's data or that the investigator exclude the subject's data from any analysis.
4. When seeking the informed consent of subjects, investigators should explain whether already collected data about the subjects will be retained and analyzed even if the subjects choose to withdraw from the research.
5. When research is covered by a certificate of confidentiality, researchers:
    a. May not disclose or provide, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains; and
    b. May not disclose or provide to any other person not connected with the research the name of such an individual or any information, document, or biospecimen that contains identifiable, sensitive information about such an individual and that was created or compiled for purposes of the research.
    c. May not utilize third parties or entities to collect or store information (e.g., contractors, online platform vendors) that cannot or will not protect against the compelled disclosure of the personally identifiable information.
    d. May disclose information only when:
        i. Required by Federal, State, or local laws (e.g., as required by the Federal Food, Drug, and Cosmetic Act, or state laws requiring the reporting of communicable diseases to State and local health departments), excluding instances of disclosure in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding; or

ii. Necessary for the medical treatment of the individual to whom the information, document, or biospecimen pertains and made with the consent of such individual; or
iii. Made with the consent of the individual to whom the information, document, or biospecimen pertains; or
iv. Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human participants in research.

e. Researchers must inform participants of the protections and limitations of certificates of confidentiality (see language in HRP-502 - TEMPLATE CONSENT DOCUMENT).
    i. For studies that were previously issued a Certificate and notified participants of the protections provided by that Certificate, NIH does not expect participants to be notified that the protections afforded by the Certificate have changed, although IRBs may determine whether it is appropriate to inform participants.
    ii. If part of the study cohort was recruited prior to issuance of the Certificate, but are no longer activity participating in the study, NIH does not expect participants consented prior to the change in authority, or prior to the issuance of a Certificate, to be notified that the protections afforded by the Certificate have changed, or that participants who were previously consented to be re-contacted to be informed of the Certificate, although the IRB may determine whether it is appropriate to inform participants.
f. Researchers conducting research covered by a certificate of confidentiality, even if the research is not federally funded, must ensure that if identifiable, sensitive information is provided to other researchers or organizations, the other researcher or organization must comply with applicable requirements when research is covered by a certificate of confidentiality.

Appendix A-2 *Additional Requirements for FDA-Regulated Research*

1. When a subject withdraws from a study:[iii]
    a. The data collected on the subject up to the point of withdrawal remains part of the study database and may not be removed.
    b. An investigator may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.
    c. If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information as described in the previous bullet, the investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). IRB approval of informed consent documents is required.
    d. If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent.
    e. An investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.
2. For FDA-regulated research involving investigational drugs:
    a. Investigators must abide by FDA restrictions on promotion of investigational drugs:[iv]
        i. An investigator, or any person acting on behalf of an investigator, must not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug.
        ii. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.
        iii. An investigator must not commercially distribute or test market an investigational new drug.
    b. Follow FDA requirements for general responsibilities of investigators[v]

i. An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.
ii. An investigator must, in accordance with the provisions of 21 CFR 50, obtain the informed consent of each human subject to whom the drug is administered, except as provided in 21 CFR 50.23 or 50.24 of this chapter.
iii. Additional specific responsibilities of clinical investigators are set forth in this part and in 21 CFR 50 and 21 CFR 56.

c. Follow FDA requirements for control of the investigational drug[vi]
   i. An investigator must administer the drug only to subjects under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator.
   ii. The investigator must not supply the investigational drug to any person not authorized under this part to receive it.
d. Follow FDA requirements for investigator recordkeeping and record retention[vii]
   i. Disposition of drug:
      1. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects.
      2. If the investigation is terminated, suspended, discontinued, or completed, the investigator must return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 21 CFR 312.59.
   ii. Case histories.
      1. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation.
      2. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital charts, and the nurses' notes. The case history for each individual must document that informed consent was obtained prior to participation in the study.
   iii. Record retention: An investigator must retain required records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed, or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.
e. Follow FDA requirements for investigator reports[viii]

i. Progress reports: The investigator must furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained.
ii. Safety reports: An investigator must promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator must report the adverse effect immediately.
iii. Final report: An investigator must provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation.
iv. Financial disclosure reports:
    1. The clinical investigator must provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under 21 CFR 54.
    2. The clinical investigator must promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

f. Follow FDA requirements for assurance of IRB review[ix]
    i. An investigator must assure that an IRB that complies with the requirements set forth in 21 CFR 56 will be responsible for the initial and continuing review and approval of the proposed clinical study.
    ii. The investigator must also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
g. Follow FDA requirements for inspection of investigator's records and reports[x]
    i. An investigator must, upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to 312.62.
    ii. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.
h. Follow FDA requirements for handling of controlled substances[xi]
    i. If the investigational drug is subject to the Controlled Substances Act, the investigator must take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

3. For FDA-regulated research involving investigational devices:
    a. General responsibilities of investigators.[xii]
        i. An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with 21 CFR 50.
    b. Specific responsibilities of investigators[xiii]
        i. Awaiting approval: An investigator may determine whether potential subjects would be interested in participating in an investigation, but must not request the written informed consent of any subject to participate, and must not allow any subject to participate before obtaining IRB and FDA approval.
        ii. Compliance: An investigator must conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.
        iii. Supervising device use: An investigator must permit an investigational device to be used only with subjects under the investigator's supervision. An investigator must not supply an investigational device to any person not authorized to receive it.
        iv. Financial disclosure:
            1. A clinical investigator must disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required under 21 CFR 54.
            2. The investigator must promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.
        v. Disposing of device: Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator must return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.
    c. Maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:[xiv]
        i. All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.
        ii. Records of receipt, use or disposition of a device that relate to:
            1. The type and quantity of the device, the dates of its receipt, and the batch number or code mark.

2. The names of all persons who received, used, or disposed of each device.
3. Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.

iii. Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital charts, and the nurses' notes. Such records must include:
1. Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent.
2. Documentation that informed consent was obtained prior to participation in the study.
3. All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
4. A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.

iv. The protocol, with documents showing the dates of and reasons for each deviation from the protocol.

v. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

d. Inspections[xv]

i. Entry and inspection: A sponsor or an investigator who has authority to grant access must permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept).

ii. Records inspection: A sponsor, IRB, or investigator, or any other person acting on behalf of such a person with respect to an investigation, must permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation.

iii. Records identifying subjects: An investigator must permit authorized FDA employees to inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not

obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.

e. Prepare and submit the following complete, accurate, and timely reports[xvi]
    i. Unanticipated adverse device effects. An investigator must submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
    ii. Withdrawal of IRB approval. An investigator must report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
    iii. Progress. An investigator must submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.
    iv. Deviations from the investigational plan:
        1. An investigator must notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency.
        2. Such notice must be given as soon as possible, but in no event later than 5 working days after the emergency occurred.
        3. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, approval by the FDA and IRB also is required.
    v. Informed consent. If an investigator uses a device without obtaining informed consent, the investigator must report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.
    vi. Final report. An investigator must, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.
    vii. Other. An investigator must, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

Appendix A-3 ***Additional Requirements for Clinical Trials (ICH-GCP)***

1. The clinical trial should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practice (GCP) and the applicable regulatory requirements. Clinical trials should be designed and conducted in ways that ensure the rights, safety, and well-being of participants.
    a. The rights, safety and well-being of the participants are the most important considerations and should prevail over interests of science and society.
    b. When designing a clinical trial, the scientific goal and purpose should be carefully considered so as not to unnecessarily exclude particular participant populations. The participant selection process should be representative of the population groups that the investigational product is intended to benefit, once authorized, to allow for generalizing the results across the broader population. Certain trials (e.g., early phase, proof of concept trials, bioequivalence studies) may not require such heterogeneous populations.
    c. A qualified physician, or when appropriate, a qualified dentist (or other qualified healthcare professionals in accordance with local regulatory requirements) should have the overall responsibility for the trial-related medical care given to and medical decisions made on behalf of participants; however, the practical interactions and the delivery of medical care and decisions can be carried out by appropriately qualified healthcare professionals in accordance with applicable regulatory requirements.
2. Clinical trials should be scientifically sound for their intended purpose and based on adequate and current scientific knowledge and approaches.
    a. The available nonclinical and clinical information on an investigational product(s) should be adequate to support the proposed clinical trial.
    b. Clinical trials should be scientifically sound and reflect the state of knowledge and experience with the investigational product(s), including, if applicable, the condition being treated, diagnosed or prevented; the current understanding of the underlying biological mechanism (of both the condition and the investigational product); and the population for which the investigational product is intended.
    c. There should be periodic review of current scientific knowledge and approaches to determine whether modifications to the trial are needed, since new or unanticipated information may arise once the trial has begun.
3. Investigator's Qualifications and Training
    a. The investigator 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 requirements, and should provide evidence of such qualifications.
    b. 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/or in other information sources provided by the sponsor.

4. Resources
    a. The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of eligible participants within the recruitment period as agreed with the sponsor.
    b. The investigator should have sufficient time, an adequate number of available and qualified staff, and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
5. Responsibilities
    a. The investigator may delegate trial-specific activities to other persons or parties. The investigator may be supported by the sponsor in the identification of a suitable service provider(s); however, the investigator retains the final decision on whether the service provider intended to support the investigator is appropriate based on information provided to the sponsor. The investigator retains the ultimate responsibility and should maintain appropriate oversight of the persons or parties undertaking the activities delegated to ensure the rights, safety and well-being of the trial participants and reliability of the data. The level of investigator oversight of the delegated activities should depend on the nature of the delegated activities and be proportionate to the importance of the data being protected and the risks to trial participant safety and data reliability.
    b. The investigator should ensure that all persons or parties to whom the investigator has delegated trial-related activities are appropriately qualified and are adequately informed about the relevant aspects of the protocol, the investigational product(s), and their assigned trial activities (including activities conducted by staff provided by other parties in accordance with local regulatory requirements). Trial-related training to persons assisting in the trial should correspond to what is necessary to enable them to fulfill their delegated trial activities that go beyond their usual training and experience.
    c. The investigator should ensure a record is maintained of the persons and parties to whom the investigator has delegated trial-related activities. Documentation of delegation should be proportionate to the significance of the trial-related activities. In situations where the activities are performed as part of clinical practice, delegation documentation may not be required.
    d. Agreements made by the investigator/institution with service providers for trial-related activities should de documented.
    e. The investigator/institution should permit monitoring and auditing by the sponsor, inspection by the appropriate regulatory authority(ies) and, in accordance with applicable regulatory requirements, review by IRB(s).
6. Communication with IRB
    a. Submission to the IRB may be made by the investigator/institution or sponsor in accordance with applicable regulatory requirements.
    b. Before initiating a trial, the investigator/institution should have a documented and dated approval from the IRB for the trial protocol, informed consent materials, participant recruitment procedures (e.g., advertisements), and any other trial-related information to be provided to participants.

c. As part of the investigator's/institution's or sponsor's (in accordance with applicable regulatory requirements) submission to the IRB, a current copy of the Investigator's Brochure or basic product information brochure should be provided. If the Investigator's Brochure or basic product information brochure is updated during the trial, the IRB should receive the current version in accordance with applicable regulatory requirements.
d. As the trial progresses, the investigator/institution or sponsor should provide any updates to the participant information to the IRB in accordance with applicable regulatory requirements.
e. The investigator or sponsor should submit documented summaries of the trial status to the IRB in accordance with local regulatory requirements or upon request.
f. The investigator or the sponsor should promptly communicate to the IRB and where applicable, to the institution any changes significantly affecting the conduct of the trial and/or increasing risk to participants.

7. Compliance with Protocol
    a. The investigator/institution should sign the protocol, or an alternative contract, to confirm agreement with the sponsor.
    b. The investigator/institution should comply with the protocol, GCP and applicable regulatory requirements.
    c. The investigator should document all protocol deviations. In addition to those identified by the investigator themselves, protocol deviations related to their trial participants and their conduct of the trial may be communicated to them by the sponsor. In either case, the investigator should review the deviations, and for those deviations deemed important, the investigator should explain the deviation and implement appropriate measures to prevent a recurrence, when applicable.
    d. The investigator should follow the protocol and deviate only where necessary to eliminate an immediate hazard(s) to trial participants. In case of deviations undertaken to eliminate immediate hazard to trial participants, the investigator should inform the sponsor promptly.
    e. The investigator should report information on the immediate hazard, the implemented change and the subsequent proposed protocol amendment, if any, to the IRB and, where applicable, regulatory authorities.
8. Premature Termination or Suspension of a Trial
    a. If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial participants and should assure appropriate therapy and follow-up for the participants.
    b. Where the investigator terminates or suspends their involvement in a trial without prior agreement by the sponsors, the investigator should promptly inform the institution, where applicable, the sponsor, the IRB, and the regulatory authorities in accordance with applicable regulatory requirements and should provide a detailed explanation of the reasons.
    c. If the sponsor terminates or suspends a trial, the investigator/institution, or the sponsor, in accordance with applicable regulatory requirement(s), should

promptly inform the IRB and the regulatory authorities and should provide an appropriate explanation.

d. If the IRB terminates or suspends its approval of a trial, the investigator should inform the institution, where applicable, and the investigator/institution should promptly notify the sponsor.

9. Participant Medical Care and Safety Reporting
    a. Medical Care of Trial Participants
        i. A qualified physician or, where appropriate, a qualified dentist (or other qualified healthcare professionals in accordance with local regulatory requirements) who is an investigator or a sub-investigator for the trial, should have the responsibility for trial-related medical care and decisions.
        ii. Other appropriately qualified healthcare professionals may be involved in the medical care of trial participants, in line with their normal activities and in accordance with local regulatory requirements.
        iii. During and following participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a participant when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.
        iv. The investigator should inform the participant's primary physician about the participant's involvement in the trial if the participant has a primary physician and agrees to the primary physician being informed.
    b. Safety Reporting
        i. Adverse events and/or abnormal test results required for safety evaluations (as outlined in the protocol) should be reported to the sponsor according to the reporting requirements and within the time periods specific in the protocol. Unfavorable medical events occurring in participants before investigational product administration (e.g., during screening) should be considered and reported to the sponsor if required by the protocol.
        ii. All serious adverse events (SAEs) should be reported immediately (after the investigator reasonably becomes aware of the event) to the sponsor. The investigator should also include an assessment of causality. In accordance with applicable regulatory requirements, the protocol may identify SAEs not requiring immediate reporting, for example, deaths or other events that are endpoints. Subsequent information should be submitted as a follow-up report, as necessary.
        iii. For reported deaths, the investigator should supply the sponsor, the IRB and, where applicable, the regulatory authority with any additional requested information (e.g., autopsy reports and terminal medical reports) when they become available.
        iv. The investigator may delegate activities for safety reporting to qualified investigator site staff but retains the overall responsibility for safety of

participants under their responsibility and compliance with the reporting requirements.

10. Informed Consent of Trial Participants
    a. In obtaining and documenting informed consent (paper or electronic format), the investigator should comply with the applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The informed consent process should include the following:
        i. Prior to consenting and enrolling participants, the investigator should have the IRB's documented approval of the informed consent materials and process;
        ii. The information should be as clear and concise as possible, use simple language and avoid unnecessary volume and complexity. This is to ensure that the trial participants or their legally acceptable representatives have an adequate understanding of the objectives of the trial, alternative treatments, potential benefits and risks, burdens, their rights, and what is expected of the participants to be able to make an informed decision as to their participant in the trial.
        iii. Varied approaches (e.g., text, images, videos and other interactive methods), may be used in the informed consent process including for providing information to the participant. The characteristics of the potential trial population (e.g., participants may lack familiarity with computerized systems) and the suitability of the method of obtaining consent should be taken into consideration when developing the informed consent materials and process. When computerized systems are used to obtain informed consent, trial participants may be given the option to use a paper-based approach as an alternative.
        iv. Obtaining consent remotely may be considered where appropriate.
        v. Whether the informed consent process takes place in person or remotely, the investigator should assure themselves of the identity of the participant (or legally acceptable representative) in accordance with applicable regulatory requirements.
    b. The participant or the participant’s legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant’s willingness to continue trial participation. The communication of this information and confirmation of the willingness to continue trial participation should be documented. New information that could impact a participant’s willingness to continue participation should be assessed to determine if re-consent is needed (e.g., depending on the stage of the trial, consideration should be given to whether the new information is relevant only to new participants or to existing participants). If re-consent is needed (e.g., information on emerging safety concerns), new information should be clearly identified in the revised informed consent materials. Revised informed consent materials should receive the IRB’s approval in advance of use.

c. Neither the investigator, nor the investigator site staff, should coerce or unduly influence a participant to participate or to continue their participation in a trial.
d. None of the information provided to the participant or the participant's legally acceptable representative during the informed consent process, should contain any language that causes the participant to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their service providers from liability for negligence.
e. The informed consent process should be conducted by the investigator or other investigator site staff delegated by the investigator, in accordance with applicable regulatory requirements. If the participant is unable to provide consent themselves (e.g., minors, patients with severely impaired decision making capacity), the participant's legally acceptable representative should provide their consent on behalf of the participant.
f. The information provided during the informed consent process and translations should be relevant, clear, simple, concise and understandable to the participant or the participant's legally acceptable representative and the impartial witness, where applicable.
g. Before informed consent may be obtained, the investigator, or investigator site staff delegated by the investigator, in accordance with the protocol and conditions of IRB approvals, should provide the participant or the participant's legally acceptable representative ample time unless justified (e.g., in an emergency situation) and opportunity to inquire about trial details and to decide whether or not to participate in the trial. Questions about the trial should be answered to the satisfaction of the participant or the participant's legally acceptable representative.
h. Prior to trial participation, the informed consent form should be signed and dated by the participant or by the participant's legally acceptable representative, where appropriate, by an impartial witness and by the investigator or delegated investigator site staff who conducted the informed consent discussion. By signing the consent form, the investigator or delegated investigator site staff attests that the informed consent was freely given by the participant or the participant's legally acceptable representative and the consent information was accurately explained to and apparently understood by the participant or the participant's legally acceptable representative. The informed consent process may involve a physical or an electronic signature and date.
i. In emergency situations, when prior consent of the participant is not possible, the consent of the participant's legally acceptable representative, if present, should be requested. When prior consent of the participant is not possible and the participant's legally acceptable representative is not possible and the participant's legally acceptable representative is not available, enrollment of the participant should require measures described in the protocol and/or elsewhere, with documented approval by the IRB, to protect the participant's rights, safety and well-being and to ensure compliance with applicable regulatory requirements. The participant or the participant's legally acceptable

representative should be informed about the trial as soon as possible, and consent as appropriate should be requested.

j. If a participant or the legally acceptable representative is unable to read, an impartial witness should be present (remotely or in-person) during the entire informed consent discussion. After the informed consent form and any other information is read and explained to the participant or the participant's legally acceptable representative, and they have orally consented to the participant's trial participation, and if capable of doing so, have signed and dated the informed consent form, the witness should sign and date the consent form. By signing the consent form, the witness attests that the consent information was accurately explained to, and apparently understood by, the participant or the participant's legally acceptable representative, and that informed consent was freely given by the participant or the participant's legally acceptable representative.

k. The informed consent discussion and the informed consent materials to be provided to participant should explain the following as applicable:
    i. The purpose of the trial;
    ii. That the trial involves research and summary of the experimental aspects of the trial;
    iii. The trial's investigational product(s) and the probability for random assignment to the investigational product, if applicable;
    iv. The trial procedures to be followed, including all invasive procedures;
    v. What is expected of the participants;
    vi. The reasonably foreseeable risks or inconveniences to the participant and, when applicable, the participant's partner, to an embryo, fetus, or nursing infant;
    vii. The reasonably expected benefits. When there is no intended clinical benefit to the participant, the participant should be made aware of this;
    viii. The alternative procedure(s) or course(s) of treatment that may be available to the participant, and their important potential benefits and risks;
    ix. The compensation and/or treatment available to the participant in the event of trial related injury;
    x. Any anticipated prorated compensation to the participant for trial participation;
    xi. Any anticipated expenses to the participant for trial participation;
    xii. That the participant's trial participation is voluntary, and the participant may decide to stop taking the investigational product or withdraw from the trial, at any time, without penalty or loss of benefits to which the participant is otherwise entitled;
    xiii. The follow-up procedure for participants who stopped taking the investigational product, withdrew from the trial or were discontinued from the trial;

xiv. The process by which the participant's data will be handled, including in the event of the withdrawal or discontinuation of participation in accordance with applicable regulatory requirements;
xv. That by agreeing to participant in the trial, the participant or their legally acceptable representative allows direct access to source records, based on the understanding that the confidentiality of the participant's medical record will be safeguarded. This access is limited for the purpose of reviewing trial activities and/or reviewing or verifying data and records by the regulatory authority(ies) and the sponsor's representatives, for example, monitor(s) or auditor(s), and in accordance with applicable regulatory requirements, IRB;
xvi. That records identifying the participant will be kept confidential and, to the extent permitted by the applicable regulatory requirements, will not be made publicly available. If the results of the trial are published, the participant's identity will remain confidential. The trial may be registered on publicly accessible and recognized databases, per applicable regulatory requirements;
xvii. That the participant or the participant's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue trial participation;
xviii. The person(s) to contact for further trial information and the trial participant's rights, and whom to contact in the event of suspected trial-related injury;
xix. The foreseeable circumstances and/or reasons under which the participant's trial participation may be terminated.
xx. The expected duration of the participant's trial participation;
xxi. The approximate number of participants involved in the trial;
xxii. That trial results and information on the participant's actual treatment, if appropriate, will be made available to them should they desire it when this information is available from the sponsor.

l. Prior to participation, the participant or the participant's legally acceptable representative should receive a copy (paper or electronic) of the signed informed consent form and any other informed consent materials provided, in accordance with applicable regulatory requirements. During trial participation, the participant or the participant's legally acceptable representative should receive a copy of the consent form updates and any other updated informed consent materials provided.
m. When a minor is to be included as a participant, age-appropriate assent information should be provided and discussed with the minor as part of the consent process, and assent from the minor to enroll in the trial should be obtained as appropriate. As process for re-consent should be considered if, during the course of the trial, the minor reaches the age of legal consent, in accordance with applicable regulatory requirements.

n. When a clinical trial includes participant who may only be enrolled in the trial with the consent of the participant's legally acceptable representative, the participants should be informed about the trial in a manner that facilitates their understanding and, if capable, the participant should sign and date the informed consent form or assent form as appropriate.

11. End of Participation in a Clinical Trial
    a. When a participant decides to stop treatment with the investigational product, stop trial visits or completely withdraw from a trial; is discontinued from the trial; or reaches the routine end of the trial, the investigator should follow the protocol and other sponsor instructions to determine appropriate follow-up measures. This may include instructions to avoid unnecessary loss of already collected critical data in accordance with applicable regulatory requirements.
    b. Although a participant is not obliged to provide a reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the participant's rights. The investigator should consider if a discussion with the participant or the participant's legally acceptable representative is appropriate. This discussion should focus on the reasons for withdrawal to determine if there are ways to address the concerns such that the participant could reconsider withdrawal without unduly influencing the participant's decision. The investigator or delegated investigator site staff should consider explaining to the participant the value of continuing their participation to minimize trial participants withdrawal. In this process, the investigator should ensure that it does not interfere with the participant's decision to refuse or withdraw participation at any time.
    c. Where relevant, the investigator should inform the participant about the trial results and treatment received when this information is available from the sponsor after unblinding, with due respect to the participant's preference to be informed.

12. Investigational Product Management
    a. Responsibility for investigational product(s), including accountability, handling, dispensing, administration and return, rests with the investigator/institution. The sponsor may facilitate aspects of investigational product management (e.g., by providing forms and technical solutions, such as computerized systems, and arranging distribution of investigational product to trial participants).
    b. When the investigator/institution delegates some or all of their activities for investigational product(s) management to a pharmacist or another individual in accordance with local regulatory requirements, the delegated individual should be under the oversight of the investigator/institution.
    c. Where the investigator has delegated activities related to investigational product management or aspects of these activities have been facilitated by the sponsor, the level of investigator oversight will depend on a number of factors, including the characteristics of the investigational product, route and complexity of administration, level of existing knowledge about the investigational product's safety and marketing status.

d. The investigator/institution and/or pharmacist or other appropriate individual, should maintain records of the product's delivery, the inventory, the use by each participant (including documenting that the participants were provided the doses specified by the protocol), and the return to the sponsor and destruction or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial participants. For authorized medicinal products, alternative approaches to the aforementioned may be considered, in accordance with local regulatory requirements.
e. The investigational product(s) should be stored as specified by the sponsor and in accordance with applicable regulatory requirement(s).
f. The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.
g. When applicable, the investigator or a person designated by the investigator/institution should explain the correct use of the investigational product(s) to each participant and should check, at intervals appropriate for the trial, that each participant is following the instructions properly.
h. The investigational product may be shipped to the participant's location or supplied to/dispensed at a location closer to the participant (e.g., at a local pharmacy or local healthcare center). The investigational product may be administered at the participant's location by investigator site staff, the participant themselves, or a caregiver or a healthcare professional.
i. Investigational product management should be arranged and conducted in accordance with applicable regulatory requirements, and safeguards should be in place to ensure product integrity, product use per protocol and participant safety.

13. Randomization Procedures and Unblinding
    a. The investigator should follow the trial's randomization procedures, if any, and in the case of an investigator-blinded trial, should ensure that the treatment randomization code is broken only in accordance with the protocol. In the case of an emergency, to protect participant safety, the investigator should be prepared and capable from the start of the trial to perform unblinding without undue delay and hinderance. The investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, emergency unblinding to protect trial participant, unblinding due to an SAE) of the investigational product(s).
14. Records
    a. In generating, recording and reporting trial data, the investigator should ensure the integrity of data under their responsibility, irrespective of the media used.
    b. The investigator/institution should maintain adequate source records that include pertinent observations on each of the trial participants under their responsibility. Source records should be attributable, legible, contemporaneous, original, accurate and complete. Changes to source records should be traceable, should not obscure the original entry and should be explained if necessary (via an audit trail). The investigator should define what is considered to be a source record(s),

the methods of data capture and their location prior to starting the trial and should update this definition when needed. Unnecessary transcription steps in between the source record and the data acquisition tool should be avoided.

c. The investigator should be provided with timely access to data by the sponsor and be responsible for the timely review of data, including relevant data from external sources that can have an impact on, for example, participant eligibility, treatment or safety (e.g., central laboratory data, centrally read imaging data, other institution's records and, if appropriate, electronic patient-reported outcome (ePRO) data. The protocol may provide exceptions for access, for instance, to protect blinding.
d. The investigator should ensure that data acquisition tools and other systems deployed by the sponsor are used as specified in the protocol or trial-related instructions.
e. The investigator should ensure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the data acquisition tools completed by the investigator site (e.g., case report form (CRF)) and in any other required reports (e.g., SAE reports). The investigator should review and endorse the reported data at important milestones agreed upon with the sponsor (e.g., interim analysis).
f. Data reported to the sponsor should be consistent with the source records or the discrepancies explained. Changes or corrections in the reported data should be traceable, should be explained (if necessary) and should not obscure the original entry.
g. The investigator/institution should implement appropriate measures to protect the privacy and confidentiality of personal information or trial participants in accordance with applicable regulatory requirements on personal data protection.
h. Data reported to the sponsor should be identified by an unambiguous participant code that can be tracked back to the identity of the participant by the investigator/institution.
i. For systems deployed by the investigator/institution that maintain and retain trial data/information, the investigator/institution should ensure that such data are protected from unauthorized access, disclosure, dissemination or alteration and from inappropriate destruction or accidental loss.
j. When using computerized systems in a clinical trial, the investigator/institution should do the following:
    i. For systems deployed by the investigator/institution, ensure that appropriate individuals have secure and attributable access;
    ii. For systems deployed by the sponsor, notify the sponsor when access permissions need to be changed or revoked from an individual;
    iii. For system deployed by the investigator/institution specifically for the purposes of clinical trials, ensure the requirements for computerized systems in section 4 of ICH GCP Annex 1[xvii] are addressed proportionate to the risks to participants and to the importance of the data;

iv. Where equipment for data acquisition is provided to trial participants by the investigator, ensure that traceability is maintained and participants are provided with appropriate training;
v. Ensure that incidents in the use and operation of computerized systems, which in the investigator/institution's judgment may have a significant and/or persistent impact on the trial data or system security, are reported to the sponsor and, where applicable, to the IRB.

k. The investigator/institution should maintain the trial records as specified in Appendix C of ICH GCP Annex 1 and as required by the applicable regulatory requirement(s). The investigator/institution should have control of all essential records generated by the investigator/institution before and during the conduct of the trial.
l. The investigator/institution should retain the essential records for the required retention period in accordance with applicable regulatory requirements or until the sponsor informs the investigator/institution that these records are no longer needed, whichever is the longest. The investigator/institution should take measures to ensure availability, accessibility and readability and to prevent unauthorized access and accidental or premature destruction of these records.
m. The investigator/institution should keep the sponsor informed of the name of the person responsible for maintaining the essential records during the retention period; for example, when the investigator site closes or an investigator leaves the site.
n. Upon request of the monitor, auditor, IRB, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

15. Reports
    a. Upon completion of the trial, the investigator, where applicable, should inform the institution. The investigator/institution should provide the IRB with a summary of the trial's outcome, and, if applicable, the regulatory authorities with any required reports.

Appendix A-4 *Additional Requirements for Department of Defense (DOD) research*

1. When appropriate, research protocols must be reviewed and approved by the IRB prior to the DOD approval. Consult with the DOD funding component to see whether this is a requirement.
2. For non-exempt Human Subjects Research, must submit to the DoD HRPO:
    a. documentation that the DoD-supported HSR has been reviewed and approved by an IRB, including scientific merit, amendments and additional reviews
    b. documentation of key investigators' human research protection training
    c. IRB approved protocol documents
    d. current FWA and IRB registration numbers
3. For research that is exempt or does not involve human subjects, must submit to the DoD HRPO:
    a. Institutional documentation of the determination that the research is either Not Human Subjects Research, exempt, or limited IRB review
    b. all protocol documents
4. Civilian researchers attempting to access military volunteers should seek collaboration with a military researcher familiar with service-specific requirements.
5. Employees of the DOD (including military and civilian temporary, part-time, and intermittent appointments) may not be able to legally accept payments to participate in research and should check with their supervisor before accepting such payments. Employees of the DOD cannot be paid for conducting research while on active duty.
6. Service members must follow their command policies regarding the requirement to obtain command permission to participate in research involving human subjects while on duty or off duty.
7. Components of the DOD might have stricter requirements for research-related injury than the DHHS regulations.
8. There may be specific educational requirements or certification required for investigators or study teams involved in DOD research.
9. When assessing whether to support or collaborate with this institution for research involving human subjects, the DOD may evaluate this institution's education and training policies to ensure the personnel are qualified to perform the research.
10. When research involves U.S. military personnel, policies and procedures require limitations on dual compensation:
    a. Federal regulations prohibit an individual from receiving pay or compensation for research during duty hours, with the exception noted in 8.c below.
    b. An individual (including military or civilian Federal employees) may be compensated for research if the participant is involved in the research when not on duty.
    c. Federal employees (including military members) while on duty and non-Federal persons may be compensated for blood draws for research up to $50 for each blood draw.

    d. Non-Federal persons may be compensated for research participation other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research.
11. Surveys performed on DOD personnel must be submitted, reviewed, and approved by the DOD Information Management Control Officer (IMCO) after the research protocol is reviewed and approved by the IRB. When a survey crosses DOD components, additional review is required. Consult the DOD funding component to coordinate this review.
12. When research involves large scale genomic data (LSGD) collected on DOD-affiliated personnel, additional protections are required:
    a. Additional administrative, technical, and physical safeguards to prevent disclosure of DOD-affiliated personnel's genomic data commensurate with risk (including secondary use or sharing of de-identified data or specimens)
    b. Research will apply an HHS Certificate of Confidentiality
    c. DOD Component security review
13. Data or information sent to a DOD component under a pledge of confidentiality for exclusively statistical purposes must be used exclusively for statistical purposes and may not be disclosed in identifiable form for any other purpose, except with the informed consent of the respondent.
14. When conducting multi-site research, a formal agreement between institutions is required to specify the roles and responsibilities of each party.
15. The following must be reported to the applicable DOD Component Office of Human Research Protections within 30 days:
    a. When significant changes to the research protocol are approved by the IRB:
        i. Changes to key investigators or institutions.
        ii. Decreased benefit or increased risk to participants in greater than minimal risk research.
        iii. Addition of vulnerable populations as participants.
        iv. Addition of DOD-affiliated personnel as participants.
        v. Change of reviewing IRB.
    b. Transfer of oversight to a different IRB
    c. When the organization is notified by any Federal body, state agency, official governing body of a Native American or Alaskan native tribe, foreign government, or other entity that any part of an HRPP is under investigation for cause involving a DOD-supported research protocol.
    d. Any problems involving risks to participants or others, suspension or termination of IRB approval, or any serious or continuing noncompliance pertaining to DOD-supported human participant research.
    e. The results of the IRB's continuing review, if required.
    f. Change in status when a previously enrolled participant becomes pregnant, or when the researcher learns that a previously enrolled participant is pregnant, and the protocol was not reviewed and approved by the IRB in accordance with 45 CFR 46, Subpart B.

g. Change in status when a previously enrolled participant becomes a prisoner, and the protocol was not reviewed and approved by the IRB in accordance with 32 CFR 219, Subpart C.
h. Closure of a DOD-supported study.
i. Must make records that document compliance or noncompliance with this issuance accessible for inspection and copying, as determined by DoD HRPP personnel, by authorized DoD representatives.

16. For human participant research that would not otherwise be approved but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates, written approval from the DOD Office for Human Research Protections must be obtained through the DOD Component Office of Human Research Protections prior to research starting.
17. Other specific requirements of the DOD research be found in the “Additional Requirements for Department of Defense (DOD) Research” section in the IRB’s HRP-318 - WORKSHEET - *Additional Federal Agency Criteria*.

Appendix A-5 *Additional Requirements for Department of Energy (DOE) Research*

(See DOE Order 443.1C, Chg 1)

1. Research that involves one or more of the following must be submitted to the appropriate IRB for human subjects research (HSR)/not HSR review and determination:
    a. Study of humans in a systematically modified environment. These studies include but are not limited to intentional modification of the human environment:
        i. Study of human environments that use tracer chemicals, particles or other materials to characterize airflow.
        ii. Study in occupied homes or offices that:
            1. Manipulate the environment to achieve research aims.
            2. Test new materials.
            3. Involve collecting information on occupants' views of appliances, materials, or devices installed in their homes or their energy-saving behaviors through surveys and focus groups.
    b. Use of social media data and/or other publicly available data about individuals or publicly available biospecimens, even if the data or biospecimens appear(s) to be de-identified. *Note: DOE follows the Health Insurance Portability and Accountability Act (HIPAA) and guidance issued by the National Institutes of Standards and Technology, as a minimum, in determining identifiability*.
    c. Human Terrain Mapping (HTM), which is managed as HSR. HTM must be strictly limited to only those projects involving the analysis and modeling of de-identified data.
2. Ensure that final HSR/not HSR determinations for studies that may constitute HSR, including exempt HSR determinations, are made through the appropriate IRB and/or IRB office. For sites that use one or both Central DOE IRB(s) as their IRB(s) of record, the Central DOE office is the responsible office and coordinates with the site HSR leads, as appropriate, to discuss project specific information and convey study determinations.
3. If you submit studies to DOE central or DOE site IRBs, complete additional DOE-specific training that includes a module on recognizing and addressing bias in the design, review and conduct of Human Research.
4. Personally identifiable information (PII) collected and/or used during HSR projects must be protected in accordance with the requirements of DOE Order 206.1, *Department of Energy Privacy Program*, current version. The Central DOE IRBs require submission of DOE's HRP- 490-CHECKLIST-Reviewing Protocols that use Personally Identifiable Information (PII) if your research includes PII. Contact the CDOE at CDOEIRB@orau.org to obtain a copy.
5. The following must be reported in writing to the DOE human subjects research Program Manager (and, when a National Nuclear Security Administration (NNSA) element is involved, the NNSA HSP Program Manager), even for HSR that meets the regulatory definition of exempt HRS as outlined in 10 Code of Federal Regulations (CFR) Part 745.104.
    a. Prior to initiation of the HSR portion of a new project, involving:

i. An institution without an established Institutional Review Board (IRB);
ii. A foreign country;
iii. The potential for significant controversy (e.g., negative press or reaction from stakeholder or oversight groups);
iv. Research subjects in a protected class (including the populations identified in Subparts B, C, and D of 45 CFR Part 46), as well as other such as individuals with impaired decision-making capability, or DOE/NNSA Federal or DOE/NNSA contractor employees as human subjects, who may be more vulnerable to coercion and undue influence to participate) that is outside of the reviewing IRB's typical range/scope; or
v. The generation or use of classified information.

b. Immediately upon a finding of a suspected or confirmed data breach involving PII in printed or electronic form, report to the IRB, the DOE/NNSA HSP Program Manager(s), and the Integrated Joint Cybersecurity Coordination Center (iJC3), in accordance with the requirements of DOE O 206.1. The appropriate HSP Program Manager must also be notified of any corrective actions taken and consulted regarding the plan for any remaining corrective actions.
c. Immediately upon learning of a serious adverse event, report to the IRB and the DOE/NNSA HSP Program Manager(s). The appropriate HSP Program Manager must also be notified of any corrective actions taken and consulted regarding the plan for any remaining corrective actions.
d. The IRB must be notified immediately and the DOE HSP Program Manager (and, when an NNSA element is involved, the NNSA HSP Program Manager) must be notified within two (2) business days of learning of the following and consulted regarding planned corrective actions if any of the following occur:
    i. Unanticipated problems, significant adverse events, and complaints about the research.
    ii. Any suspension or termination of IRB approval of research.
    iii. Any known or potential incidents of non-compliance with requirements of DOE Order 443.1C, Chg.1, 10 CFR Part 745, or 45 CFR Part 46..

6. Requirements for human participant protections for classified research apply to all classified research conducted or supported by the DOE and its national laboratories, including contracts, and including Human Terrain Mapping research.
7. Researchers conducting human subjects research in any other country or on citizens or other individuals residing in that country must be cognizant of country-specific human subjects research requirements and consult the IRB regarding applicability of such requirements.
8. No human subjects research conducted with DOE funding, at DOE institutions (regardless of funding source)[xviii], or by DOE or DOE contractor personnel (regardless of funding source or location conducted), whether done domestically or in an international environment, including classified and proprietary research, may be initiated without both a Federalwide Assurance (FWA) or comparable assurance (e.g., Department of Defense assurance) of compliance and approval by the cognizant Institutional Review Board (IRB) in accordance with 10 CFR 745.103.

9. Human subjects research involving multiple DOE sites (e.g., members of the research team from more than one DOE site and/or data or human subjects from more than one DOE site) must be reviewed and approved by one of the Central DOE IRBs prior to initiation, or if authorized by the DOE and/or NNSA HSP Program Manager, other appropriate IRB of record. In all cases, an IRB Authorization Agreement (IAA) or Memorandum of Understanding (MOU) must be in place between the organization(s) conducting the HSR and the organization responsible for IRB review.
10. Human subjects research that involves targeted inclusion of DOE Federal and/or contractor employees or their data must first be reviewed and approved by the appropriate DOE IRB (the DOE site IRB or one of the Central DOE IRBs), or if deemed more fitting by the Federally assured DOE site or Headquarters, other appropriate IRB of record, in accordance with an IAA or MOU negotiated between the DOE site or Headquarters and the organization responsible for IRB review.
11. Classified and unclassified intelligence and intelligence-related HSR regardless of the funding source (including, but not limited to, Strategic Intelligence Partnership Program (SIPP) funded studies, DOE Office of Intelligence and Counterintelligence (DOE-IN) funded studies, and/or studies funded by other DOE program offices that use intelligence datasets), must be reviewed and approved by the Central DOE IRB-Classified.
12. If applicable, federally funded HSR must comply with the requirements of the Paperwork Reduction Act.
13. If applicable, HSR involving visiting student researchers, researchers, and scholars from other countries as members of research teams must comply with Department of State requirements, e.g., those outlined in 22 CFR Part 62, *Exchange Visitor Program*, and *U.S. Department of State Guidance Directive 2024-01*, current version.
14. Equitable payment of human subjects participating in HSR is allowable.
15. Other specific requirements of the DOE research can be found in the “Additional Requirements for Department of Energy (DOE) Research” section in the IRB’s HRP-318 - WORKSHEET - Additional Federal Agency Criteria.

Appendix A-6 *Additional Requirements for Department of Justice (DOJ) Research*

Additional Requirements for DOJ Research conducted in the Federal Bureau of Prisons

1. Implementation of Bureau programmatic or operational initiatives made through pilot projects is not considered to be research.
2. The project must not involve medical experimentation, cosmetic research, or pharmaceutical testing.
3. The research design must be compatible with both the operation of prison facilities and protection of human subjects.
4. Investigators must observe the rules of the institution or office in which the research is conducted.
5. Any investigator who is a non-employee of the Bureau of Prisoners must sign a statement in which the investigator agrees to adhere to the requirements of 28 CFR 512.
6. The research must be reviewed and approved by the Bureau Research Review Board.
7. Incentives cannot be offered to help persuade inmate subjects to participate. However, soft drinks and snacks to be consumed at the test setting may be offered. Reasonable accommodations such as nominal monetary recompense for time and effort may be offered to non-confined research subjects who are both:
    a. No longer in Bureau of Prisons custody, and
    b. Participating in authorized research being conducted by Bureau employees or contractors.
8. A non-employee of the Bureau may receive records in a form not individually identifiable when adequate advance written assurance is provided to the agency that the record will be used solely as statistical research or reporting.
9. Except as noted in the consent statement to the subject, you must not provide research information that identifies a subject to any person without that subject's prior written consent to release the information. For example, research information identifiable to a particular individual cannot be admitted as evidence or used for any purpose in any action, suit, or other judicial, administrative, or legislative proceeding without the written consent of the individual to whom the data pertain.
10. Except for computerized data records maintained at an official Department of Justice site, records that contain non-disclosable information directly traceable to a specific person may not be stored in, or introduced into, an electronic retrieval system.
11. If you are conducting a study of special interest to the Office of Research and Evaluation but the study is not a joint project involving Office of Research and Evaluation, you may be asked to provide Office of Research and Evaluation with the computerized research data, not identifiable to individual subjects, accompanied by detailed documentation. These arrangements must be negotiated prior to the beginning of the data collection phase of the project.
12. Required elements of disclosure additionally include:
    a. Identification of the investigators.

b. Anticipated uses of the results of the research.
c. A statement that participation is completely voluntary and that the subject may withdraw consent and end participation in the project at any time without penalty or prejudice (the inmate will be returned to regular assignment or activity by staff as soon as practicable).
d. A statement regarding the confidentiality of the research information and exceptions to any guarantees of confidentiality required by federal or state law. For example, an investigator may not guarantee confidentiality when the subject indicates intent to commit future criminal conduct or harm himself or herself or someone else, or, if the subject is an inmate, indicates intent to leave the facility without authorization.
e. A statement that participation in the research project will have no effect on the inmate subject's release date or parole eligibility.

13. You must have academic preparation or experience in the area of study of the proposed research.
14. The IRB application must include a summary statement, which includes:
    a. Names and current affiliations of the investigators.
    b. Title of the study.
    c. Purpose of the study.
    d. Location of the study.
    e. Methods to be employed.
    f. Anticipated results.
    g. Duration of the study.
    h. Number of subjects (staff or inmates) required and amount of time required from each.
    i. Indication of risk or discomfort involved as a result of participation.
15. The IRB application must include a comprehensive statement that includes:
    a. Review of related literature.
    b. Detailed description of the research method.
    c. Significance of anticipated results and their contribution to the advancement of knowledge.
    d. Specific resources required from the Bureau of Prisons.
    e. Description of all possible risks, discomforts, and benefits to individual subjects or a class of subjects, and a discussion of the likelihood that the risks and discomforts will actually occur.
    f. Description of steps taken to minimize any risks.
    g. Description of physical or administrative procedures to be followed to:
        i. Ensure the security of any individually identifiable data that are being collected for the study, and
        ii. Destroy research records or remove individual identifiers from those records when the research has been completed.
    h. Description of any anticipated effects of the research study on institutional programs and operations.

    i. Relevant research materials such as vitae, endorsements, sample consent statements, questionnaires, and interview schedules.
16. The IRB application must include a statement regarding assurances and certification required by federal regulations, if applicable.
17. You must assume responsibility for actions of any person engaged to participate in the research project as an associate, assistant, or subcontractor.
18. At least once a year, you must provide the Chief, Office of Research and Evaluation, with a report on the progress of the research.
19. At least 12 working days before any report of findings is to be released, you must distribute one copy of the report to each of the following: the chairperson of the Bureau Research Review Board, the regional director, and the warden of each institution that provided data or assistance.
20. You must include an abstract in the report of findings.
21. In any publication of results, you must acknowledge the Bureau's participation in the research project.
22. You must expressly disclaim approval or endorsement of the published material as an expression of the policies or views of the Bureau.
23. Prior to submitting for publication the results of a research project conducted under this subpart, you must provide two copies of the material, for informational purposes only, to the Chief, Office of Research and Evaluation, Central Office, Bureau of Prisons.
24. Other specific requirements of the Department of Justice (DOJ) Research Conducted within the Federal Bureau of Prisons (BOP) can be found in the “Additional Requirements for Department of Justice (DOJ) Research Conducted within the Federal Bureau of Prisons (BOP)” section in the IRB’s HRP-318 - WORKSHEET - Additional Federal Agency Criteria.

Additional Requirements for DOJ Research Funded by the National Institute of Justice

1. The project must have a privacy certificate approved by the National Institute of Justice Human Subjects Protection Officer.
2. All investigators and research staff are required to sign employee confidentiality statements, which are maintained by the responsible investigator.
3. The confidentiality statement on the consent document must state that confidentiality can only be broken if the subject reports immediate harm to subjects or others.
4. Under a privacy certificate, investigators and research staff do not have to report child abuse unless the subject signs another consent document to allow child abuse reporting.
5. A copy of all data must be de-identified and sent to the National Archive of Criminal Justice Data, including copies of the informed consent document, data collection instruments, surveys, or other relevant research materials.
    a. At least once a year, the researcher shall provide the Chief, Office of Research and Evaluation, with a report of the progress of the research.
    b. At least 12 working days before any report of findings is to be released, the researcher shall distribute one copy of the report to each of the following: the chairperson of the Bureau Research Review Board, the regional director, and the

warden of each institution that provided data or assistance. The researcher shall include an abstract in the report of findings.

c. In any publication of results, the researcher shall acknowledge the Bureau's participation in the research project.
d. The research shall expressly disclaim approval or endorsement of the published material as an expression of the policies or views of the Bureau.
e. Prior to submitting for publication the results of a research project conducted under this subpart, the researcher shall provide two copies of the material, for informational purposes only, to the Chief, Office of Research and Evaluation, Central Office, Bureau of Prisons

6. Other specific requirements of the Department of Justice (DOJ) Research Funded by the National Institute of Justice can be found in the “Additional Requirements for Department of Justice (DOJ) Research” section in the IRB’s HRP-318 - WORKSHEET - Additional Federal Agency Criteria.

Appendix A-7 *Additional Requirements for Department of Education (ED) Research*

1. Each school at which the research is conducted must provide an assurance that they comply with the Family Educational Rights and Privacy Act (FERPA) and the Protection of Pupil Rights Amendment (PPRA).
2. Provide a copy of all surveys and instructional material used in the research. Upon request, parents of children[xix] involved in the research[xx] must be able to inspect these materials.
3. The school in which the research is being conducted must have policies regarding the administration of physical examinations or screenings that the school may administer to students.
4. Other specific requirements of the Department of Education (ED) Research can be found in the “Additional Requirements for Department of Education (ED) Research” section in the IRB’s HRP-318 - WORKSHEET - Additional Federal Agency Criteria.

Appendix A-8 *Additional Requirements for Environmental Protection Agency (EPA) Research*

1. Research conducted, supported, or intended to be submitted to EPA is subject to Environmental Protection Agency regulations.
2. Intentional exposure of pregnant women or children to any substance is prohibited in any research conducted, supported, or intended to be submitted to EPA.
3. Observational research involving pregnant women and fetuses are subject to additional DHHS requirements for research involving pregnant women (45 CFR 46 Subpart B) and additional DHHS requirements for research involving children (45 CFR 46 Subpart D.)
4. Research involving children must meet category #1 or #2, i.e., research not involving greater than minimal risk or research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.
5. Other specific requirements of Environmental Protection Agency (EPA) research can be found in the “Additional Requirements for Environmental Protection Agency (EPA) Research and Research Intended to be Submitted to the Environmental Protection Agency” section in the IRB’s HRP-318 - WORKSHEET - Additional Federal Agency Criteria.

Appendix A-9 *Additional Requirements for Veterans Administration (VA) Research*

- VA research is research that is conducted by researchers (serving on VA compensated, Without Compensation (WOC) appointment, or Intergovernmental Personnel Act (IPA) appointment) while on VA time or on VA property. The research may be funded by VA, by other sponsors, or be unfunded. VA research must have Research and Development (R&D) Committee approval before it is considered VA Research and before it can be initiated. All research activities approved by the R&D Committee are considered VA Research.
    - VA-affiliated nonprofit research and education corporations (NPC) are authorized by Congress under 38 U.S.C. 7361-7366 to provide flexible funding mechanisms for the conduct of research and education at one or more VA facilities. Research approved by a facility R&D Committee are considered to be a VA research project or a VA education activity, regardless of the source of funding, the entity administering the funds, or the research or education site (see VHA Handbook 1200.17, Department of Veterans Affairs Nonprofit Research and Education Corporations Authorized by Title 38 U.S.C. Sections 7361 Through 7366, dated April 27, 2016 and revised May 9, 2017).
    - VA research includes VA-approved research conducted at international sites not within the United States, its territories, or Commonwealths, and includes research where human tissues are sent outside the United States.
- The investigator must give first priority to the protection of research subjects, uphold professional and ethical standards and practices, and adhere to all applicable VA and other federal requirements, including the local VA facility's policies and procedures regarding the conduct of research and the protection of human subjects. The investigator must hold a current VA appointment to conduct VA research.
- The responsibilities of the investigator may be defined in the protocol or IRB application. Specifically, the principal investigator's and local site investigator's responsibilities include, but are not limited to:
    - Qualifications to Conduct Human Subjects Research. VA investigators must have the appropriate training, education, expertise, and credentials to conduct the research according to the research protocol.
        - PIs must ensure that all research staff are qualified (e.g., including but not limited to appropriate training, education, expertise, and credentials) to perform procedures assigned to them during the course of the study.
        - Investigators and their staff conducting human subjects research must be credentialed and privileged as required by current local and VA requirements (see VHA Handbook 1100.19, *Credentialing and Privileging*, and VHA Directive 2012-030, *Credentialing of Health Care Professionals*, or successor policies). Investigators and their research staff may only perform those activities in a research study for which they have the relevant credentials and privileges.

    - Investigators and co-investigators must be identified on the IRB application and must provide credentials, conflict of interest statements or other documentation required by VA and local facility policies.
    - All individuals involved in conducting VA human subjects research are required to complete training in ethical principles on which human subjects research is to be conducted. Specific requirements regarding the type and frequency of training are found on ORD's website. All other applicable VA and VHA training requirements at the local and national level must be met (e.g., privacy and information security training).
    - Investigators must prospectively document their research with their supervisor in writing.
    - Investigators must submit exempt protocols that require limited IRB review to the IRB for limited IRB review/approval.
- Research Protocol. The investigator must develop and submit a research protocol that is scientifically valid, describes the research objectives, background and methodology, provides for fair and equitable recruitment and selection of subjects, minimizes risks to subjects and others, and describes a data and safety monitoring plan consistent with the nature of the study. The research must be relevant to the health or welfare of the Veteran population. When relevant, the protocol must include the following safety measures:
    - The type of safety information to be collected, including AEs;
    - Frequency of safety data collection;
    - Frequency or periodicity of review of cumulative safety data;
    - Statistical tests for analyzing the safety data to determine if harm is occurring; and
    - Conditions that trigger an immediate suspension of the research, if applicable.
- Approvals. The investigator must submit the protocol for initial review and obtain written approvals from the IRB, other applicable committees, and the R&D Committee. In addition, the investigator must receive written notice from the ACOS/R&D that the research may commence before initiating the research.
    - An investigator may not self-certify that a study is exempt.
    - Once approved by the IRB, the protocol must be implemented as approved. All modifications to the approved research protocol or consent form must be approved by the IRB prior to initiating the changes except when necessary to eliminate apparent immediate hazards to the subject.
    - The investigator must also obtain continuing review and approval at a frequency established by the IRB, but not less than once every year (except for research subject to the 2018 Requirements where continuing review is not required), and is expected to submit all materials required for continuing review in sufficient time to assure approval prior to the expiration date. No research activities may be conducted at any time without a currently valid IRB approval.
- Conflict Of Interest. The investigator must disclose to the IRB any potential, actual, apparent, or perceived conflict of interest of a financial, professional, or personal

nature that may affect any aspect of the research, and comply with all applicable VA and other federal requirements regarding conflict of interest.

- Initial Contact. During the recruitment process, members of the research team must make initial contact with potential subjects in person or by letter prior to initiating any telephone contact, unless there is written documentation that the subject is willing to be contacted by telephone about the study in question or a specific kind of research as outlined in the study. (NOTE: This does not apply to situations where a Veteran calls in response to an advertisement. If existing information from sources such as a medical record or database, research or non-research, are used to identify human subjects, there must be an IRB approved HIPAA waiver for this activity in the new protocol.)
  - Any initial contact by letter or telephone must provide a telephone number or other means that the potential subject can use to verify that the study constitutes VA research.
  - If a contractor makes the initial contact by letter, the VA investigator must sign the letter.
- Informed Consent for Research. The investigator must obtain and document legally effective informed consent of the subject or the subject's LAR prospectively (i.e., no screening or other interaction or intervention involving a human subject can occur until after the IRB-approved informed consent requirements have been met) that is in alignment with ethical principles that govern informed consent for research. The only exceptions are if the IRB determines the research is exempt, or approves a waiver of the informed consent process, or approves a waiver of the signed informed consent document.
  - If the investigator does not personally obtain informed consent, the investigator must delegate this responsibility in writing (e.g., by use of a delegation letter) to research staff sufficiently knowledgeable about the protocol and related concerns to answer questions from prospective subjects, and about the ethical basis of the informed consent process and protocol.
    - If the investigator contracts with a firm, e.g., a survey research firm, to obtain consent from subjects, collect private individually identifiable information from human subjects, or be involved in activities that would institutionally engage the firm in human subjects research, the firm must have its own IRB oversight of the activity. In addition, the Privacy Officer must determine that there is appropriate authority to allow the disclosure of individual names and other information to the contracted firm.
    - The investigator must ensure that all original signed and dated informed consent documents are maintained in the investigator’s research files, readily retrievable, and secure.
  - HIPAA Authorization. The investigator or designee must obtain HIPAA authorization for the use and disclosure of the subject’s PHI, or obtain an IRB-approved waiver of HIPAA authorization unless there is a limited data set and appropriate DUA. The written HIPAA authorization may either be a standalone document or combined with the research informed consent approved by the IRB.

If a standalone document is used as the written HIPAA authorization, VA Form 10-0493: Authorization for Use and Release of Individually Identifiable Health Information Collected for VHA Research, must be used to document the authorization.

- Reporting. The investigator is responsible for reporting any unanticipated problems involving risks to subjects or others, apparent serious or continuing noncompliance, any termination or suspension of research, and privacy or information security incidents related to VA research, including: any inappropriate access, loss, or theft of PHI; noncompliant storage, transmission, removal, or destruction of PHI; or theft, loss, or noncompliant destruction of equipment containing PHI, in accordance with local facility or IRB SOPs and VHA Directive 1058.
    - VA personnel who become aware of the occurrence of research-related events (as described above) are responsible for following VA medical facility established processes and timelines for promptly reporting the events to the appropriate VA medical facility point(s)-of-contact designated to receive such reports at the VA medical facility that approved the research.
- Research Records. All written information given to subjects must be in the investigator's research file along with the consent form(s). All records regardless of format (paper, electronic, electronic systems) must be managed per the National Archives and Records Administration (NARA) approved records schedules found in VHA Records Control Schedule (RCS) 10-1 and therefore must be retained until disposition instructions, as approved by NARA, are published in VHA RCS 10-1. NOTE: Once the disposition schedule is determined, records should be disposed in accordance with VHA RCS 10-1. If the investigator leaves VA, all research records must be retained by the VA facility where the research was conducted.
- VHA Health Record. A VHA health record must be created or updated, and a progress note created, for all research subjects (Veterans or Non-Veterans) who receive research procedures or interventions as inpatients or outpatients at VA medical facilities that are either used in, or may impact the medical care of, the research subject at a VA medical facility or at facilities contracted by VA to provide services to Veterans (e.g., Community-Based Outpatient Clinics or nursing homes). Informed consent and HIPAA authorization documents are not required to be in the health record. The name and contact information of the researcher conducting the study should be included.
- Investigational Drugs and Devices. The investigator must conduct VA human subjects research involving investigational drugs and devices in accordance with all applicable VA policies and other federal requirements including, but not limited to: VHA Directive 1200.05 (3), VHA Handbook 1108.04, and applicable FDA regulations. The storage and security procedures for test articles used in research must be reviewed and approved by the IRB and follow all applicable federal rules.
    - The PI or Local Site Investigator (LSI) must provide the Pharmacy Service with the following:

- Written approval letter signed by the ACOS for R&D that all relevant approvals have been obtained and that the study may be initiated at the site (VHA Directive 1200.01);
- An IRB approval letter;
- A copy of the approved study protocol;
- A copy of VA Form 10-9012, Investigational Drug Information Record, when appropriate;
- An Investigator Brochure (IB), when appropriate;
- Any sponsor-provided documents relating to the storage, preparation, dispensing, and accountability of the investigation products;
- Copies of all correspondence addressed to the Researcher from the FDA specific to the investigational drugs as appropriate;
- A copy of the consent document for each participating participant with all appropriate signatures;
- Protocol revisions, amendments, and updates after IRB approval and after the IRB approved the amendment;
- Updates and changes to authorized prescribers after IRB approval;
- Documentation of IRB continuing review approval;
- Notice, in writing, to the Chief, Pharmacy Service, the research pharmacy when applicable, the IRB, and the Research and Development Committee when a study involving investigational drugs has been suspended, terminated, or closed.

- The PI or LSI must provide Pharmacy Service and/or the Research Service Investigational Pharmacy, investigational drug information on each patient receiving an investigational drug, through the electronic medical record or other locally-approved means. This documentation is to include allergies, toxicities, or adverse drug events related to the investigational drug, or the potential for interaction with other drugs, foods, or dietary supplements (e.g., herbals, nutriceuticals).
- The PI or LSI must place the completed VA Form 10-9012, or electronic equivalent, in the subject's medical record.
- The PI must comply with all dispensing and documentation requirements and the dispensing log must be made accessible to the investigational drug pharmacist upon request.

- Initiation of Research Projects. IRB approval is for a specified time period based on the degree of risk of the study, not to exceed 1 year except for research subject to the 2018 Requirements where continuing review is not required. The IRB determines the expiration date based upon its date of review and communicates that date to the investigator in the written approval letter. The investigator must not initiate the IRB-approved research protocol until all applicable requirements in VHA Directive 1200.01 have also been met, including obtaining R&D Committee approval.
- Expiration of IRB Approval. There is no provision for any grace period to extend the conduct of research beyond the expiration date of IRB approval. Therefore,

continuing review and re-approval of research must occur on or before the date when IRB approval expires. If approval expires, the investigator must:
    - Stop all research activities including, but not limited to, enrollment of new subjects, analyses of individually identifiable data, and research interventions or interactions with currently participating subjects, except where stopping such interventions or interactions could be harmful to those subjects; and
    - Immediately submit to the IRB Director a list of research subjects who could be harmed by stopping specified study interventions or interactions. The IRB Director, in conjunction with the IRB Chair, must determine within 2 business days whether or not such interventions or interactions may continue.
  - Documentation of Informed Consent
    - When documentation of informed consent is not waived by IRB, the investigator or designee must ensure that the informed consent document is signed and dated by the subject or the subject's legally authorized representative,
    - If consent is obtained electronically, the following must be met:
      - Authentication controls on electronic consent provide reasonable assurance that such consent is rendered by the proper individual; and
      - The subject dates the consent or the software provides the current date when signed.
- Vulnerable Subjects
  - The following populations are considered categorically vulnerable and have specific VA requirements for their inclusion in research:
    - Pregnant Women, Human Fetuses and Neonates
    - Prisoners
    - Children
    - Subjects who lack decision-making capacity
- Research Involving Prisoners
  - Research involving prisoners cannot be conducted by VA investigators while on official VA duty, at VA facilities, or at VA-approved off-site facilities unless a waiver has been granted by the CRADO.
  - Waiver requests must be submitted electronically to the CRADO by the VA medical facility Director with the following documents:
    1. A letter from the VA medical facility Director supporting the conduct of the VA study involving prisoners;
    2. Rationale for conducting the research involving prisoners, to include additional ethical protections taken by the proposed research to ensure prisoners can make voluntary and uncoerced decisions whether or not to participate as subjects in research;
    3. Documentation of the VA investigator's qualifications to conduct the research involving prisoners, such as a biosketch and a list of all research team members;
    4. Location of institutions where the research is proposed to be conducted;
    5. A copy of the IRB approval letter specifically documenting its review determinations according to 45 CFR 46.305(a);

6. A copy of the IRB minutes approving the research with documentation that at least one member of the IRB included a prisoner or a prisoner representative for the review of the research;
7. A copy of the IRB-approved research study;
8. A copy of the IRB-approved informed consent document; and
9. A copy of the written HIPAA authorization.

- If such a waiver is granted, the research must comply with the requirements of 45 CFR 46.301 - 46.306.

- Research Involving Children
  - Research involving children must not present greater than minimal risk.
  - The VA medical facility Director must approve participation in the proposed research that includes children.
  - Research involving biological specimens or data obtained from children is considered to be research involving children even if de-identified. If the biological specimens or data were previously collected, they must have been collected under applicable policies and ethical guidelines.
  - The IRB must have the appropriate expertise to evaluate VA research involving children and must comply with the requirements of 45 CFR 46.401 - 46.404 and 46.408.
- Research Involving Pregnant Women, Human Fetuses and Neonates as Subjects
  - Neonates: Interventional research enrolling neonates cannot be conducted by VA investigators while on official duty, or at VA facilities, or at VA approved off-site facilities. VA investigators may conduct research involving noninvasive monitoring of neonates if the research is determined by the IRB to be minimal risk. Prospective observational and retrospective record review studies that involve neonates or neonatal outcomes are permitted. The VA medical facility Director must certify that the medical facility has sufficient expertise in neonatal health to conduct the proposed research.
  - Pregnant Women: The VA medical facility Director must certify that the medical facility has sufficient expertise in women's health to conduct the proposed research if the research includes interventional studies or invasive monitoring of pregnant women as subjects.
  - Research that involves provision of in vitro fertilization services can be conducted by VA investigators while on official VA duty, at VA facilities, or at VA-approved off-site facilities. This includes prospective and retrospective research involving provision of or the enhancement of FDA-approved methods of in vitro fertilization for studies involving consenting subjects, both male and female, undergoing or who have undergone in vitro fertilization for the treatment of certain forms of human infertility. In vitro fertilization is any fertilization of human ova that occurs outside the body of a female, either through a mixture of donor human sperm and ova or by any other means.
  - Prospective and retrospective studies that enroll or include pregnant subjects who conceived through in vitro fertilization or other artificial reproductive technologies are permitted.

- Research that uses human fetal tissue or that focuses on either a fetus, or human fetal tissue, in-utero or ex-utero cannot be conducted by VA investigators while on official VA duty, at VA facilities, or at VA-approved off-site facilities. Use of stem cells shall be governed by the policy set by NIH for recipients of NIH research funding.

- Research Involving Persons Who Lack Decision-Making Capacity
  - The protocol must include a plan, that it is appropriate given the population and setting of the research, for how investigators will determine when a legally authorized representative will be required to provide informed consent. In general, the research staff must perform or obtain and document a clinical assessment of decision-making capacity for any subject suspected of lacking decision-making capacity.
  - When the potential subject is determined to lack decision-making capacity, investigators must obtain consent from the LAR of the subject (i.e., surrogate consent). NOTE: Investigators and IRBs have a responsibility to consult with the Office of General Counsel (OGC) regarding state or local requirements for surrogate consent for research that may supersede VA requirements.
  - The following persons are authorized to consent on behalf of persons who lack decision-making capacity in the following order of priority:
    - (1) Health care agent (i.e., an individual named by the subject in a Durable Power of Attorney for Health Care);
    - (2) Legal guardian or special guardian;
    - (3) Next of kin: a close relative of the patient 18 years of age or older, in the following priority: spouse, child, parent, sibling, grandparent, or grandchild; or
    - (4) Close friend.
  - If feasible, the investigator must explain the proposed research to the prospective research subject even when the legally authorized representative gives consent. Although unable to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may a subject be forced or coerced to participate in a research study even if the LAR has provided consent.
  - Legally authorized representatives must be told that their obligation is to try to determine what the subjects would do if able to make an informed decision. If the potential subjects' wishes cannot be determined, the legally authorized representatives must be told they are responsible for determining what is in the subjects' best interest.
- Research Involving Certificates of Confidentiality (CoC)
  - If information about the subject's participation will be included as part of the VHA medical record, information must be given to the prospective subject as part of the informed consent process that information regarding study participation will be included in the medical record.
  - In instances where a written informed consent form is used, inclusion of a statement that the study has been issued a CoC is required.
  - Investigators should work with the research office in their facility to assure that when Veterans are enrolled in a study protected by a CoC, they are not simultaneously

enrolled in other interventional studies unless it is absolutely clear that this enrollment does not raise safety issues.

- Collaborative Research
  - This addresses collaborations between VA and non-VA investigators. Collaboration is encouraged when VA investigators have a substantive role in the design, conduct, and/or analysis of the research. VA may also serve as a Coordinating Center for collaborative studies. NOTE: Collaborative studies do not include studies conducted under a CRADA with pharmaceutical companies or other for-profit entities.
  - IRB of Record Approval. Each institution is responsible for safeguarding the rights and welfare of human subjects and providing oversight of the research activities conducted at that institution.
    - Each collaborating institution engaged in human subjects research must obtain approval from its IRB of Record and hold a FWA or another assurance acceptable to VA, e.g., DoD assurance.
    - VA investigators must submit a protocol or other documentation to their VA IRB of Record that delineates which research activities will be conducted by VA.
    - Each institution engaged in the collaborative research must use the informed consent document and HIPAA authorization required by their respective institutional policies for subjects recruited from that institution, or procedures requiring participation of the subject at that institution. The informed consent document may contain information on the project as a whole, as long as the document clearly describes which procedures will be performed at VA and which will be performed at other institutions.
      - The VA informed consent document must clearly state when procedures mentioned at other institutions are part of the VA's portion of the study.
      - The informed consent document and HIPAA authorization must be consistent and include information describing the following:
        - PHI to be collected and/or used by the VA research team;
        - PHI to be disclosed to the other institutions; and
        - Purpose for which the PHI may be used.
  - Waivers. PHI obtained in research for which the IRB of Record has waived the requirements to obtain a HIPAA authorization and a signed informed consent document may not be disclosed outside VA unless the VA facility Privacy Officer ensures and documents VA's authority to disclose the PHI to another institution. A waiver of HIPAA authorization is not sufficient to fulfill the requirements of other applicable privacy regulations such as the Privacy Act of 1974 (5 U.S.C. 552a).
  - Research Data. The protocol, addendum, and/or IRB of Record application must describe the data to be disclosed to collaborators, the entity(ies) to which the data are to be disclosed, and how the data are to be transmitted. This includes data from individual subjects as well as other data developed during the research such as the analytic data and the aggregate data.
    - Each VA facility must retain a complete record of all data obtained during the VA portion of the research in accordance with privacy requirements, the Federal Records Act, and VHA Records Control Schedule (RCS) 10-1.

    - All disclosures and data transmission must meet privacy and security requirements per VA Directive 6500, VHA Handbook 6500, and VHA Directive 1605.1.
  - Written agreements. Collaborative research involving non-VA institutions may not be undertaken without a signed written agreement (e.g., a CRADA or a Data Use Agreement (DUA)) that addresses such issues as the responsibilities of each party, the ownership of the data, and the reuse of the data for other research. NOTE: Any reuse must be consistent with the protocol, the informed consent document, and the HIPAA authorization.
- Photography, Video and/or Audio Recording for Research Purposes
  - The informed consent for research must include information describing any photographs, video, and/or audio recordings to be taken or obtained for research purposes, how the photographs, video, and/or audio will be used for the research, and whether the photographs, video, and/or audio will be disclosed outside the VA.
    - An informed consent to take a photograph, video, and/or audio recording cannot be waived by the IRB.
    - The consent for research does not give legal authority to disclose the photographs, video, and/or audio recordings outside the VA. A HIPAA authorization is needed to make such disclosures.
- International Research
  - VA international research is defined as any VA-approved research conducted at international sites (i.e., not within the United States (U.S.), its territories, or Commonwealths), any VA-approved research using either identifiable or de-identified human biological specimens or identifiable or de-identified human data originating from international sites, or any VA-approved research that entails sending such specimens or data out of the U.S. This definition applies regardless of the funding source (funded or unfunded) and to research conducted through any mechanism of support including MOUs, CRADAs, grants, contracts, or other agreements. NOTE: Research conducted at U.S. military bases (including bases outside the U.S.), on U.S. ships, or at U.S. embassies is not considered international research.
    - Sending specimens or data to individuals with VA appointments at international sites (e.g., a WOC appointment, a VA investigator on sabbatical at an international site) is considered international research. Remote use of data that is maintained on VA computers within the U.S. or Puerto Rico and accessed via a secure connection is not considered international research.
    - International research includes multi-site trials involving non-U.S. sites where VA is the study sponsor, a VA investigator is the overall study-wide PI, VA holds the Investigational New Drug (IND), or the VA manages the data collection and the data analyses.
    - International research does not include studies in which VA is only one of multiple participating sites where the overall study-wide PI is not a VA investigator (i.e., the PI for the study as a whole is not a VA investigator).
  - Before approving international research involving human subjects research, the IRB must ensure that human subjects outside of the U.S. who participate in research

projects in which VA is a collaborator receive equivalent protections as research participants inside the U.S. (see OHRP guidance at http://www.hhs.gov/ohrp/international/index.html). NOTE: The VA medical facility Director must approve participation in the proposed international research.
    - All international research must also be approved explicitly in a document signed by the VA medical facility Director, except for Cooperative Studies Program activities which must be approved by the CRADO.
- Use Preparatory to Research
    - VA investigators may use individually-identifiable health information to prepare a research protocol prior to submission of the protocol to the IRB for approval without obtaining a HIPAA authorization or waiver of authorization.
        - VA investigators must not arbitrarily review PHI based on their employee access to PHI until the investigator documents the following required information as "Preparatory to Research" in a designated file that is readily accessible for those required to audit such information (e.g., Health Information Manager or PO):
            - Access to PHI is only to prepare a protocol;
            - No PHI will be removed from the covered entity (i.e., VHA); and
            - Access to PHI is necessary for preparation of the research protocol.
        - Non-VA researchers may not obtain VA information for activities preparatory to research without appropriate VA approvals (see VHA Directive 1605.01).
        - During the preparatory activities, the VA investigator:
            - Must only record aggregate data. The aggregate data may only be used for background information to justify the research or to show that there are adequate numbers of potential subjects to allow the investigator to meet enrollment requirements for the research study;
            - Must not record any individually identifiable health information; and
            - Must not use any individually identifiable information to recruit research subjects.
        - Preparatory activities can include reviewing database output (computer file or printout) containing identifiable health information generated by the database owner if the investigator returns the database output to the database owner when finished aggregating the information.
        - Contacting potential research subjects and conducting pilot or feasibility studies are not considered activities preparatory to research.
        - Activities preparatory to research only encompass the time to prepare the protocol and end when the protocol is submitted to the IRB.
- Posting of Clinical Trial Consent Forms
    - For studies subject to the 2018 Requirements, if a VA research study is a clinical trial, one IRB-approved informed consent form must be posted by either the investigator or the Federal department or agency conducting or supporting the study, unless the IRB waived documentation of informed consent. The consent form must be posted after the clinical trial is closed to recruitment and no later than 60 days after the last study visit by any subject as described in the IRB-approved protocol. For multi-site studies, it applies when the entire study has

closed to subject recruitment. Any proprietary or personal information (such as names and phone numbers) must be redacted prior to posting the informed consent form.
    - For any ORD-funded clinical trial, the applicable ORD funding service will be responsible for posting the informed consent form.
    - For a clinical trial funded or supported by a Federal agency or department other than VA, the awardee is responsible for posting the informed consent form.
    - For a clinical trial funded or supported by a non-Federal agency or department (e.g., university, industry, nonprofit organization) or not funded, the VA Investigator conducting the clinical trial is responsible for ensuring that the informed consent form is posted. If the clinical trial includes multiple sites engaged in the clinical trial, an agreement must exist specifying who is responsible for posting the informed consent form.
- Other specific requirements of Veterans Administration (VA) research can be found in the "Additional Requirements for Veterans Administration (VA) Research" section in the IRB's HRP-318 – WORKSHEET – *Additional Federal Agency Criteria*.

Appendix A-10 ***Single IRB Studies***

1. The National Institutes of Health (NIH) expects that all sites participating in NIH-funded, multi-site studies involving non-exempt human subjects research will use a single Institutional Review Board (sIRB) to conduct the ethical review required by the Department of Health and Human Services regulations for the Protection of Human Subjects at 45 CFR Part 46.
    a. This policy applies to the domestic sites of NIH-funded multi-site studies where each site will conduct the same protocol involving non-exempt human subjects research, whether supported through grants, cooperative agreements, contracts, or the NIH Intramural Research Program. It does not apply to career development, research training or fellowship awards.
    b. This policy applies to domestic awardees and participating domestic sites. Foreign sites participating in NIH-funded, multi-site studies will not be expected to follow this policy.
    c. Requests for exceptions that are not based on a legal, regulatory, or policy requirement will be considered if there is a compelling justification for the exception. The NIH will determine whether to grant an exception following an assessment of the need. NIH will consider exception requests for studies subject to the NIH Single IRB Policy if they are NOT also subject to the revised Common Rule (rCR) cooperative research sIRB provision.
2. The Office for Human Research Protections expects that all sites located in the U.S. participating in cooperative research will rely upon approval by a single IRB for that portion of the research that is conducted in the U.S. The reviewing IRB will be identified by the Federal department or agency supporting or conducting the research, or proposed by the lead institution subject to the acceptance of the Federal department or agency supporting the research.

    The following research is not subject to this provision:

    a. Cooperative research for which more than single IRB review is required by law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe); or
    b. Research for which any Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context.
    c. For research not subject to paragraph (b) of this section, an institution participating in a cooperative project may enter into a joint review arrangement, rely on the review of another IRB, or make similar arrangements for avoiding duplication of effort.

Appendix A-11 *Additional Requirements for Research Subject to EU General Data Protection Regulations (GDPR)*

1. Human Research involving personal data about individuals located in (but not necessarily citizens of) European Union member states, Norway, Iceland, Liechtenstein, and Switzerland is subject to EU General Data Protection Regulations.
2. For all prospective Human Research subject to EU GDPR, contact institutional legal counsel or your institution's Data Protection Officer to ensure that the following elements of the research are consistent with institutional policies and interpretations of EU GDPR:
    a. Any applicable study design elements related to data security measures.
    b. Any applicable procedures related to the rights to access, rectification, and erasure of data.
    c. Procedures related to broad/unspecified future use consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens.
3. Where FDA or DHHS regulations apply in addition to EU GDPR regulations, ensure that procedures related to withdrawal from the research, as well as procedures for managing data and biospecimens associated with the research, remain consistent with Appendices A-1 and A-2 above.

Appendix A-12 *Continuity Planning for Investigators Conducting Human Research*

Investigators conducting human research should be aware of the following additional considerations associated with managing Human Research during an emergency, disaster, or other disruptive event (e.g., extreme weather events, natural disasters, man-made disasters, infectious disease pandemics, loss or failure of facilities, significant and unexpected loss of funding and/or workforce, etc.) related to investigators' ongoing interactions with research subjects and the institutional review board (IRB) in such cases.

During Emergency/Disruption: Deciding Whether a Study-Specific Risk Mitigation Plan for Ongoing Research Is Needed

In general, investigators should develop a study-specific emergency/disruption risk mitigation plan for their research unless one of the following is true:

- Research does not involve in-person interaction with research subjects.
- Research can be conducted as written while adhering to additional institution-level and HRPP-level guidance and requirements regarding the emergency/disruption event.
- The research is externally sponsored, and the sponsor has developed a protocol-specific risk mitigation plan for the research.
- The research has been voluntarily placed on hold for recruitment and all research procedures (except for necessary follow-up procedures to be done consistently with additional institution-level and HRPP-level guidance and requirements regarding the emergency/disruption event).

Tools and Resources for Developing Study-Specific Emergency/Disruption Risk Mitigation Plans for Ongoing Research

Review HRP-108 - FLOWCHART - *Study-Specific Emergency-Disruption Risk Mitigation Planning* and HRP-351 - WORKSHEET - *Protocol-Specific Emergency-Disruption Risk Mitigation Planning* for general guidance on developing study-specific risk mitigation plans.

Voluntary Holds on Human Research Activities

Investigators may voluntarily elect to place all recruitment, enrollment and research procedures on temporary hold during emergency/disruption scenarios if doing so will better ensure the safety of research subjects and would not create any additional risks to the safety and welfare of research subjects. Such voluntary holds on research activity do not require IRB notification or review.

Submitting Study-Specific Emergency/Disruption Risk Mitigation Plans for IRB Review

If immediate modification of the research is necessary to eliminate an apparent immediate hazard to a subject, take action and notify the IRB within five business days, using the standard pathway to submit reportable new information.

For all other study modifications made to ensure the ongoing safety of research subjects during emergency/disruption scenarios, submit a study amendment and all relevant new or modified study materials to the IRB.

Other Reportable New Information Considerations During Emergency/Disruption Scenarios

The IRB's list of reportable events includes two items for which additional clarification and guidance may be helpful during emergency/disruption scenarios:

- ***Failure to follow the protocol due to the action or inaction of the investigator or research staff.*** Emphasis on action or inaction of the investigator or research staff has been added because this requirement does not include action or inaction of the research subject. For example, study teams may notice an increase in the number of subjects who do not arrive for scheduled research visits under emergency/disruption circumstances. Failure of a research participant to appear for a scheduled research visit is not noncompliance due to action or inaction by the investigator or research staff, and therefore does not require reporting to the IRB.
- ***Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject.*** During emergency/disruption scenarios, there will be cases where there is sufficient time to obtain IRB approval of any proposed modifications to previously approved research, and in such cases, investigators should follow standard IRB procedures for submitting modifications. However, there will be other cases where investigators must make more immediate changes to the protocol or investigational plan to minimize or eliminate immediate hazards or to protect the life and well-being of research participants. Such changes may be implemented without IRB approval but are required to be reported to the IRB within five business days afterward in accordance with IRB policies and procedures for submitting reportable new information.

[i]This document satisfies AAHRPP element I.1.A, I.1.C-I.1.F, I-3, I.4.C, I.5.C, I.5.D, I.6.B, I.7.A-I.7.C, I-9, II.2.A, II.2.C, II.2.G, II.2.E-II.2.E.2, II.2.F-II.2.F.3, II.2.I, II.3.C-II.3.C.1, II.3.E, II.3.F, II.3.G, II.4.A, II.4.B, II.5.A, II.5.B, III.1.A, III.1.B, III.1.D, III.1.E, III.1.F, III.2.A, III.2.C, III.2.D

[ii] http://www.hhs.gov/ohrp/policy/subjectwithdrawal.html

[iii] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126489.pdf

[iv] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.7

[v] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.60

[vi] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.61

[vii] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.62

[viii] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.64

[ix] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.66

[x] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.68

[xi] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.69

[xii] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.100

[xiii] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.110

[xiv] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.140

[xv] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.145

[xvi] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.150

[xvii] https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106.pdf

[xviii] HSR conducted by researchers from outside institutions at/using DOE/NNSA user facility capabilities may only be initiated if the researchers have provided documentation of study-specific approval or exemption determination from the IRB/ethics board used by their institution.
If the outside institutions using DOE facility capabilities are not funded by DOE, partnering with any DOE or DOE contractor organization, or using DOE or DOE contractor employees or employee data, their studies will not be expected to comply with all other requirements in this order unless the DOE/NNSA site responsible for the user facility requires such compliance.

[xix] Children are persons enrolled in research not above the elementary or secondary education level, who have not reached the age or majority as determined under state law.

[xx] Research or experimentation program or project means any program or project in any research that is designed to explore or develop new or unproven teaching methods or techniques.