



UNIVERSITY *of* MARYLAND
THE FOUNDING CAMPUS

Investigator Manual

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What is purpose of this manual?

This document “INVESTIGATOR MANUAL” is designed to guide you through policies, procedures and resources related to the conduct of Human Research that are specific to University of Maryland Baltimore. All human research related activities must be in full compliance with current UMB HRPP and IRB policies and procedures while maintaining compliance with the Federal regulations and assuring the protection of human research participants.

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 does my staff and I need in order to conduct Human Research?](#)”

Throughout this document “organization” refers to University of Maryland, Baltimore. Please refer to “[SOP: Definitions](#)” for additional definitions.

UMB’s Human Research Protections Program (HRPP)

This organization’s Human Research Protection Program (HRPP) is a comprehensive system to ensure the protection of the rights and welfare of participants in Human Research. The Human Research Protection Program is based on all the individuals in this organization along with key individuals and committees fulfilling their roles and responsibilities described in this plan. Please refer to “[UMB HUMAN RESEARCH PROTECTION PROGRAM PLAN.](#)”

Federalwide Assurance (FWA)

The UMB HRPP maintains a current Federalwide Assurance ([FWA, 00007145](#)) (UMB signed Assurance Document) which obligates the Institution to uphold ethical principles and is applicable whenever research is conducted or supported by any U.S. federal department or agency that has adopted the U.S. Federal policy for the Protection of Human Subjects (also known as the Common Rule), unless exempt.

UMB’s Institutional Review Board (IRB)

The UMB’s Institutional Review Board (IRB) functions independently, although in coordination with other organizational entities in its role in protecting human research participants. No organizational official or entity at any level can approve research that has not been reviewed and approved by an IRB. Refer to “[HUMAN RESEARCH PROTECTION PROGRAM PLAN.](#)”

Human Research Protections Office (HRPO)

The Human Research Protections Office (HRPO) is the coordinating office for the HRPP and IRB. It is located within the Office of Academic Affairs-Research Compliance and reports to the Institutional Official. Refer to “[HUMAN RESEARCH PROTECTION PROGRAM PLAN.](#)” You can access the HRPO website via <http://umaryland.edu/hrp>.

Comprehensive, Institutional Collaborative Evaluation of Research On-line (CICERO)

The UMB HRPP maintains a web-based electronic system for creating, submitting, routing, signing, reviewing, and tracking research protocols. You can access CICERO via <http://cicero.umaryland.edu>.

What is Human Research?

The document “[UMB HUMAN RESEARCH PROTECTION PROGRAM PLAN](#)” defines the activities that this organization considers to be “Human Research” as defined in DHHS regulations at [45 CFR §46.102\(d\)](#) and [45 CFR §46.102\(f\)](#) and as defined in FDA regulations at [21 CFR §56.102\(c\)](#), [21 CFR §56.102\(e\)](#), and [21 CFR §812.3\(p\)](#). An algorithm for determining whether an activity is Human Research can be found in the “[WORKSHEET: Human Research Determination](#).” 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 IRB determination that the Human Research is Exempt). If you have questions about whether an activity is Human Research, request a determination from the Human Research Protections Office (HRPO) via CICERO. See below “[How do I submit new Human Research to the IRB?](#)” Also, see below “[What are the different regulatory classifications that research activities may fall under?](#)”

What is the Human Research Protection Program?

The document “[UMB HUMAN RESEARCH PROTECTION PROGRAM PLAN](#)” describes this organization’s overall plan to protect participants in Human Research:

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

When am I engaged in research?

You are considered “engaged” in human participants’ research when you 1) intervene or interact with living individuals for research purposes, or 2) obtain individually identifiable private information for research purposes. Further, a site is considered to be “engaged” in human participants’ research when it receives a direct Federal award to support the research. See “[WORKSHEET: Engagement Determination](#)”

Can I be a principal investigator for a study?

To qualify as a principal investigator, you must be a full-time (>51% effort) faculty member holding one of the following titles at UMB:

- Professor
- Associate Professor
- Assistant Professor

If you do not hold one of the above positions and wish to become a principal investigator, you must submit a written request with justification and your curriculum vitae for consideration by the Institutional Official. Contact:

Name: Julie Doherty, RN, MSN
Title: Director, Human Protections Administrator
620 W. Lexington Street, Second Floor
Baltimore, Maryland 21201
Email: jdoherty@umaryland.edu
(410) 706-3867

This request must also include a written agreement from a faculty member who meets the requirements of a principal investigator to mentor you on the conduct of human subject research. Students and fellows are not permitted to be Principal Investigators.

If you hold one of the above listed positions and you wish to become a principal investigator, email your request to hrpo@umaryland.edu. Include in the email your full name, department, division, email address, and your current faculty position. When your information has been validated, the principal investigator role will be added to your CICERO account and you will be notified via email.

The IRB recognizes one Principal Investigator for each project. The Principal Investigator bears the ultimate responsibility for assuring that the conduct of the study complies with all UMB HRPP policies and procedures for the protection of human participants.

When the Principal Investigator for clinical studies involving medical/clinical interventions or investigational agents does not have a medical degree (M.D.), there must be at least one sub-investigator on the project that is a qualified M.D. with the appropriate expertise for the study.

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

All individuals involved in the design, conduct and/or reporting of research must be adequately qualified and licensed relevant to the scope and complexity of the research conducted and their role in the research.

All individuals involved in the design, conduct and/or reporting of research must be familiar with and know how to apply the ethical principles of *The Belmont Report*, current Federal and State laws and regulations, current institutional policies and procedures, and [Good Clinical Practice standards](#) (See [Appendix A](#)) when conducting research involving humans at UMB. For more information and resources, please visit the UMB HRP website at <http://umaryland.edu/hrp>.

All individuals involved in the design, conduct and/or reporting of research must complete the online Collaborative Institutional Training Initiative (CITI) human participants online training program as well as HIPAA training. IRB approval will not be granted for proposed research in which the principal investigator has not completed the required human research protections training and HIPAA training listed below. The principal investigator of each research project is responsible for ensuring that all individuals involved in the design, conduct and/or reporting of the research have also completed the required training.

The CITI site can be accessed at www.citiprogram.org. This training is valid for a three-year period, after which time a refresher CITI course must be completed. A minimum score of 80% overall must be obtained for CITI training.

All UMB employees are required to complete HIPAA 125 training. In addition, individuals involved in the design, conduct and/or reporting of research are required to complete HIPAA 201 training. Both of these trainings can be accessed at <http://somvweb.som.umaryland.edu/hipaa/quiz/index.asp>.

If you are conducting VA research, you and your research team that are involved in the design, conduct and/or reporting of the research project must also complete the annual VA requirements for research. Contact the VA Research Service for specific details: 410-605-7000 x7030.

Individuals that are external to the UMB system and are involved in the design, conduct and/or reporting of research conducted at UMB must have completed their employer's required certifications or trainings. External Investigators must supply their CV and proof of the required certifications or trainings to the UMB Principal Investigator under which they are working. The UMB Principal Investigator will be responsible for forwarding these to the HRPO Office when requested.

What are my obligations as a Principal Investigator when developing a research project?

- Make sure that you have the adequate resources to protect the rights, welfare and safety of human participants involved in the research, including:
 - Sufficient time to conduct, oversee and complete research
 - Adequate number of qualified staff
 - A process to ensure that all persons involved in the design, conduct and/or reporting of research are adequately informed about the protocol and their research-related duties and functions
 - Adequate facilities in which to perform study procedures
 - Availability of medical or psychological resources that participants may need as a consequence of the research
 - Access to a population that will allow recruitment of the necessary number of participants.
- Make sure that the research application is consistent with the proposal for funding for extramural or intramural support.
- Act as a liaison between the IRB and the research sponsor (e.g., notification of IRB review and approval).
- Make sure that there are additional protections for research involving vulnerable populations as required.
- If your research involves entities within UMB that are not under your control, you must ensure appropriate communication, education, and training of those staff.
- Refer to the Center for Clinical Trials and Corporate Contracts (CCT) website for information regarding correct research billing procedures: <http://umaryland.edu/cct>
- If your research is sponsored by a commercial sponsor, please refer to the Corporate Contracts section of the CCT website: <http://umaryland.edu/cct>
- If your research is sponsored by a federal agency, foundation or other non-profit organization, please see Sponsored Program Administration section on the Research @ UMB website: <http://umaryland.edu/ord/>
- If your research involves investigational drugs, biologics, or devices, you must follow “[SOP: Control of Investigational Test Articles.](#)”

How do I know what federal regulations apply to my research?

Your research may be regulated by more than one federal agency, depending on the project funding and type of project. Regardless of funding source, all human participant research must meet the regulatory criteria for approval. See “[WORKSHEET: Criteria for Approval and Additional Considerations](#).”

- If your research is funded by a federal agency, you are required to follow Department of Health and Human Services (DHHS) regulations at [45 CFR 46](#). Also refer to [Appendix A](#) for more information.
- If your research involves drugs or devices, you are required to follow Food and Drug Administration (FDA) regulations at 21 CFR 50 and 21 CFR 56. Also refer to [Appendix A](#) for more information.
- If your research involves the use of a drug with an active Investigational New Drug (IND) application, you are required to follow FDA regulations at 21 CFR 312. Also refer to [Appendix A](#) for more information.
 - If you are the IND holder, you are required to follow both the Investigator responsibilities and Sponsor responsibilities at 21 CFR 11, 21 CFR 54, 21 CFR 210, 21 CFR 312, 21 CFR 314, 21 CFR 320, 21 CFR 330, and 21 CFR 601.
- If your research involves the use of a device with an active Investigational Device Exception (IDE), you are required to follow FDA regulations at 21 CFR 812. Also refer to [Appendix A](#) for more information.
 - If you are the IDE holder, you are required to follow both the Investigator responsibilities and Sponsor responsibilities at 21 CFR 11, 21 CFR 54, 21 CFR 812, 21 CFR 814, 21 CFR 820, and 21 CFR 860.
- If your research involves the use of veterans, Veterans Health Administration (VHA) funding or other VA resources, you are required to follow regulations in VHA Handbook 1200.05. Also refer to [Appendix A](#) for more information.
- If your research involves funding by a federal agency other than DHHS and NIH, you are required to follow regulations pertaining to those agencies:
 - Department of Defense – see [Appendix A](#)
 - Department of Energy – see [Appendix A](#)
 - Department of Education – see [Appendix A](#)

Does the IRB charge a fee to review research proposals?

Yes, the IRB charges to review certain research proposals for Industry-Supported Applications. Contact the [Center for Clinical Trials and Corporate Contracts](#) office for further information.

How do I submit new Human Research to the IRB?

Complete a CICERO application, attach all required documents and submit to the HRPO. If you are unsure if the project is human participants research, refer to “[WORKSHEET: Human Research Determination](#)”

All research proposals require a CICERO application.

How do I complete the CICERO Application?

- Abbreviated Title: Enter the abbreviated title. This is the title that will appear in the CICERO application
- Full Title: Enter the full protocol name. This title will be entered into the determination letter.
- Select Type of Submission: Select the appropriate type of submission. Refer to the “Help” button for descriptions of types of submissions.
- Application: Select whether or not you have an existing research protocol. This can be a sponsor’s protocol or other type of protocol that has all of the required information. See below “[How do I write an Investigator Protocol?](#)”

Complete the remaining sections in the application as appropriate. Remember that if you have an existing protocol, you can reference sections or page numbers of that protocol in the CICERO application. Read all of the instructions for each section. Provide all the information requested, as appropriate for the research protocol.

Research Team

- Principal Investigator – Name the person with overall responsibility for the conduct of the Human Research. There can only be one investigator with this overall responsibility. If you are not listed on the Principal Investigator drop-down list, see above section “[Can I be a principal investigator for a study?](#)” to determine if you meet the criteria for Principal Investigator privileges. If you meet the criteria, please contact HRPO at 410-706-5037 or hrpo@umaryland.edu for assistance.
- Point of Contact – Who is the alternative point of contact for the Principal Investigator. This person can be a study coordinator or any other study team member. In case the IRB cannot contact the Principal Investigator, this person is a secondary person to contact. A person listed as Point of Contact (POC) cannot also be listed under “Other Team Members.”
- Other Team Members – List all Human Research personnel involved in the design, conduct, or reporting of the Human Research and their roles. This includes all co-investigators, sub-investigators, coordinators, assistants, students, and collaborators who have a role in the design, conduct, or reporting of the Human Research.

When adding each person, you must select whether or not to give “edit rights.” Selecting “yes” will allow the person to edit the online forms and to execute activities (protocol modifications, reportable events, etc) in CICERO. Note: granting a person edit rights will automatically add them to the email CC list and this person will receive all emails from CICERO to the team regarding the submission. In addition, for each person added, you must select whether or not they will receive emails sent to the Principal Investigator by CICERO and the HRPO.

Each person who is added to the protocol must complete a Conflict of Interest statement. CICERO will send each person an email. Individuals must update their Conflict of Interest statement within 10 days of the becoming aware of any change in a financial interest that affects this statement. The principal investigator is responsible for ensuring that all investigators and research staff comply with this requirement. When there are questions about the qualifications of research team members, the Organizational Official can be consulted and make determinations about further actions.

Approvals Required Prior to Initiating Research Check

all additional approvals that are required:

- Radiation being used for reasons other than clinical care
- The use of any biohazards
- Research involving human gene transfer or immune response
- Research involving cancer
- Research using VA patients, facilities or personnel

Department Scientific and Feasibility Review

All new research submissions must undergo Department Scientific and Feasibility Review. If your research involves a department other than your department, a specialty review must also be completed. For example, your research involves children (review required from the Department of Pediatrics) or cancer (review required from the Greenebaum Cancer Center). CICERO will send reviews to these departments automatically when you submit the application. When the Department Chair is the principal investigator (PI), the Department Scientific and Feasibility Review must be completed by an individual outside of the PI's department.

How do I write an Investigator Protocol?

All research submissions must either have a completed application form in CICERO or a separate research protocol attached and referenced in CICERO. Follow the application instructions in CICERO. If you have a sponsor's protocol, you may reference pages in the sponsor's protocol in the corresponding sections of the CICERO application. Here are some key points to remember when completing the CICERO application or creating your own separate research protocol document:

- For an Investigator Protocol document:
 - the italicized bullet points in the templates serve as a guide to investigators when developing an Investigator Protocol for submission to the IRB. All italicized comments are meant to be deleted prior to submission.
 - Note that, depending on the nature of your research, certain sections of the template may not be applicable to your Investigator Protocol. Skip these sections as appropriate.
- You may not involve any individuals who are members of the following populations as participants in your research unless you indicate this in your inclusion criteria as the inclusion of participants in these populations requires additional protections. Students and employees may be enrolled like any other vulnerable population. CICERO will provide additional information and requirements for these vulnerable populations:
 - Adults unable to consent
 - Individuals who are not yet adults (infants, children, teenagers)
 - Pregnant women
 - Prisoners
 - Employees
 - Students

How do I create a consent document?

Use the “[TEMPLATE CONSENT DOCUMENT](#)” to create a consent document. Note that all consent documents must contain all of the required and all additional appropriate elements of informed consent disclosure. Review section 7 of the “[WORKSHEET: Criteria for Approval and Additional Considerations](#)” to ensure that these elements are addressed. For research involving the VA, you must use a VA consent form, VA 10-1086.

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 the IRB’s “[WORKSHEET: Criteria for Approval and Additional Considerations](#),” to ensure that these elements are addressed. When using the short form of consent documentation, the appropriate signature block from “[TEMPLATE CONSENT DOCUMENT](#)” should be used on the short form.

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

What if I want to enroll non English speaking participants in my study?

Participants who do not speak English should be presented with informed consent documents in a



language understandable to them that includes all the required and additional elements for disclosure. Either the long form of the consent document needs to be translated in writing into the subject's language or the short form of consent document may be used. With the short form of consent documentation, the long form of consent may be translated orally and only a small portion of the information translated into the subject's language.

Please see below "[How do I document consent?](#)" and the requirement for the short form consent on "[WORKSHEET: Short Form of Consent Documentation.](#)"

Can I recruit subjects over the phone for my study?

Ensuring Appropriate Telephone Contact with Subjects. This pertains to contacting the subject by telephone. Research team members are prohibited from requesting Social Security numbers by telephone.

- **Initial Contact.** During the recruitment process, ensuring the research team makes initial contact with the potential subject 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 (e.g., if the potential subject has diabetes, the subject may indicate a desire to be notified of any diabetes-related research studies) or the IRB has determined otherwise, with appropriate justification. NOTE: One source of information about clinical trials that can be shared with potential subjects is the NIH clinical trials Web site (<http://www.clinicaltrials.gov>) where clinical trials are listed.
- **Later Contact.** Ensuring the research team begins telephone calls to the subject by referring to previous contacts and, when applicable, the information provided in the informed consent form, and ensuring that the scope of telephone contacts with the subject is limited to topics outlined in IRB approved protocols and informed consent forms.

When can a consent waiver be used?

The IRB may approve a consent procedure which does not include, or which alters, some or all of the required elements of informed consent. Refer to "[CICERO CHECKLIST: Waiver or Alteration of the Consent Process.](#)" Also, the IRB may approve a consent procedure which waives the requirements to obtain written informed consent entirely. Refer to "[CICERO CHECKLIST: Waiver of Written Documentation of the Consent Process.](#)"

When can a HIPAA waiver be used?

The Health Insurance Portability and Accountability Act (HIPAA) regulates how protected health information can be used and disclosed. An investigator must obtain an authorization via a HIPAA Authorization Form from all participants in research prior to the use or disclosure of protected health information (PHI) for any research related purpose. PHI is any information in the medical

record or designated record set that can be used to identify an individual. In addition, refer to “[WORKSHEET: HIPAA Authorizations for Research](#)” for elements required in a HIPAA Authorization Form.

The IRB can waive or alter the requirement for HIPAA Authorization for study recruitment purposes or for the entire study. Refer to “[CICERO CHECKLIST: HIPAA Waiver of Authorization](#).”

When do I have to register my project at ClinicalTrials.gov?

Certain research projects are required to register at the website ClinicalTrials.gov. These projects are also responsible to update records and report results per policy. Refer to: “[HRP-095 - SOP Clinical Trials](#)” and “[ClinicalTrials.gov Instructions for the Research Community](#)”.

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 DHHS or FDA definition of “research” involving “human participants” for the activity to fall under IRB oversight. Activities that meet neither definition of “Research” involving “Human Participants” are not subject to IRB oversight or review. Refer to “[WORKSHEET: Human Research Determination](#).” Contact the Human Research Protections Office (HRPO) in cases where it is unclear whether an activity meets the regulatory definition of Human Research. When a project is determined to be nonhuman subject research, that determination is made by the particular information provided in the CICERO application. If you make any changes to the project, you must submit a protocol modification to determine if the project remains nonhuman participant research.
- Exempt: Certain categories of Human Research may be exempt from regulation but require IRB review. It is the responsibility of the IRB, not the investigator, to determine whether Human Research is exempt from IRB review. Refer to “[CICERO CHECKLIST: Pre-Review and Administrative Review](#)” for reference on the categories of research that may be exempt. When a research study is determined to be exempt, that determination is made on the particular information provided in the CICERO application. If you make any changes to an exempt study, you must submit a protocol modification to determine if the research study continues to meet the exemption status.
- Review Using the Expedited Procedure: Certain categories of non-exempt Human Research may qualify for review using the expedited procedure. Refer to “[CICERO CHECKLIST: Pre-Review and Administrative 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 the IRB requires specific modifications to the research before approval can be finalized. See section below “[What will happen after IRB review?](#)”
- Deferred: Made when the IRB determines that it is unable to approve research and the IRB has recommendations that might make the protocol approvable. When this motion is made, the IRB describes its reasons and recommendations. See section below “[What will happen after IRB review?](#)”
- 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 this motion is made, the IRB describes its reasons. See section below “[What will happen after IRB review?](#)”
- Tabled: Made when the IRB cannot approve the research at a meeting for reasons unrelated to the research, such as loss of quorum. These are often administrative reasons. When taking this action, the IRB automatically schedules the research for review at a future meeting.

How does the IRB decide whether to approve Human Research?

The criteria for IRB approval can be found in “[WORKSHEET: Criteria for Approval and Additional Considerations](#)” for non-exempt Human Research. The latter worksheet references other checklists that might be relevant. All checklists and worksheets can be found on the HRPO Web site.

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

YOU ARE ENCOURAGED TO USE THE CHECKLISTS AND WORKSHEETS 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 determination indicating that the IRB has approved the Human Research, requires modifications to secure approval, or has deferred, tabled, or disapproved the Human Research.

The IRB can approve a research project for no more than 365 days. The Federal regulations make no provision for any grace period extending the conduct of research beyond the expiration date of IRB approval; therefore, continuing review and re-approval of research must occur before the date when IRB approval expires. If this does not happen, all research activities must cease. See section below “[What do I do if my study expires?](#)”

- If the IRB has approved the Human Research: The Human Research may commence once all other organizational approvals have been met. IRB approval is 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 as soon as possible via CICERO. If all requested modifications are made, the IRB will issue a final approval. Research cannot commence until this final approval is received. If you do not respond to the IRB within 30 days, the offer of approval with the requested modifications will be withdrawn. If you do not accept the modifications, write up your response and submit it to the IRB within 30 days. If you do not provide additional information or correspondence within 30 days, and the IRB will require a complete new submission.
- If the IRB defers the Human Research: The IRB will provide a statement of the reasons for deferral and any recommendations that might make the protocol approvable. Make the recommended changes and respond to each of the IRB’s questions/concerns and submit them to the IRB as soon as possible via CICERO. Once a complete response has been received, the submission will be scheduled for review at an IRB meeting.
- If the IRB disapproves the Human Research: The IRB will provide a statement of the reasons for disapproval. If the investigator wishes to pursue the research project, a new CICERO application must be submitted.

In all cases, you have the right to address your concerns to the IRB directly at an IRB meeting. To request this, contact the Director, Regulatory Compliance.. You may address the IRB panel via teleconference.

Does my research need to be reviewed by committees other than the IRB?

Depending on the type of research you do, where it is done, what procedures are involved and other factors, your research proposal may need to be reviewed by a committee in addition to the IRB. Some of these required approvals will be captured by your CICERO application.

For VA research the investigators must submit the appropriate documentation to the VA R&D Committee for initial review and approval. Investigators must also submit modification documentation to the VA R&D committee for review and approval for any modifications related to biosafety or radiation safety.

What are my obligations as a Principal Investigator after IRB approval?

- Do not start Human Research activities until you have the final IRB approval letter (including washout and screening).
- Do not start Human Research activities until you have the approval of departments or divisions that require approval prior to commencing research that involves their resources. CICERO will automatically send notification to the required departments from the questions you answer within your CICERO application. You will be able to see the department's responses in CICERO's history log for your study.
- Do not start Human Research activities until organizational approvals are met. See "Approvals Required Prior to Initiating Research".
- Personally conduct or supervise the Human Research.
 - Protect the rights, safety, and welfare of participants involved in the research.
 - 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.
 - Assure that each participant is adequately informed and freely consents to participate in the in the research, unless a waiver of consent has been obtained from the UMB IRB. The Principal Investigator must personally assure that every reasonable precaution is taken to reduce risks to participants.
 - Delegate responsibility to the research staff in accordance with the staff's training and qualifications.
 - Assure that all procedures associated with the research are performed, with the appropriate level of supervision, only by individuals who are licensed or otherwise qualified to perform them under the laws of Maryland and polices of the University of Maryland, Baltimore.
 - Monitor the research study and perform quality management activities to ensure the protection of participants and the quality of the research data. Deficiencies

identified during quality improvement processes must be addressed in a timely manner. Refer to “[CHECKLIST: Investigator Quality Improvement Assessment](#)” for more information.

- Do not modify the Human Research without prior IRB review and approval unless necessary to eliminate apparent immediate hazards to participants.
 - Changes in approved research that are initiated without IRB approval to eliminate apparent immediate hazards to the participant are promptly (within 5 days) reported to the IRB and are reviewed by the IRB to determine whether each change was consistent with ensuring the participants’ continued welfare.
- Submit to the IRB:
 - Proposed modifications as described in this manual. See below “[How do I submit a modification?](#)”
 - A continuing review application no later than 6 WEEKS PRIOR to the expiration date found in the IRB approval letter for your study. See below “[How do I submit a continuing review?](#)”
 - A closure report when the Human Research is closed. See below “[How Do I Close Out a Study?](#)”
- Do not accept or provide payments to professionals in exchange for referrals of potential participants (“finder’s fees.”)
- Do not accept payments designed to accelerate recruitment that were tied to the rate or timing of enrollment (“bonus payments.”)
- Be open to participants’ complaints or requests for information. Investigators and research staff should follow a process to respond appropriately to such complaints.
 - Notify the IRB of any participant or other individual’s complaints regarding the research. The complaint may be reported at continuing review if it involves no risk to the participants or others or does not change the risk/benefit analysis (e.g., a participant complains that he/she does not like the investigator’s clinic hours and subsequently withdraws from the research).
 - Report complaints that involve potential risks to participants or others or result in a possible change in the risk/benefit analysis as an unanticipated problem as soon as possible, but no later than FIVE WORKING DAYS after the investigator first learns of the complaint (e.g., a member of the research team where the research is conducted complains that the research assistant has not maintained her research notes in a confidential manner which may have potentially breached confidentiality).
- See additional requirements of various federal agencies in Appendix A.

How do I document consent?

Consent to participation in research is documented by the use of an informed consent document that has been signed by the participant or the participant's legally authorized representative. Use the signature block approved by the IRB. Complete all items in the signature block. Refer to "[SOP: Informed Consent Process for Research](#)" and "[SOP: Written Documentation of Consent](#)."

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 required by the IRB the subject's or representative's signature is to be witnessed by an individual who signs and dates the consent document.
- For participants 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.
- For Veterans Administration (VA) research, consent must be documented on a Veterans Administration (VA) Form 10-1086.

The following are the requirements for short form consent documents:

- The subject or representative signs and dates the consent document.
- The individual obtaining consent signs and dates the summary.
- The witness to the oral presentation signs and dates the consent document and the summary. The person obtaining consent may not be the witness to the consent.
- A copy of the signed and dated consent document and a copy of the signed and dated summary are to be provided to the person signing the document.
- For Veterans Administration (VA) research, consent must be documented on a Veterans Administration (VA) Form 10-1086.

What needs to be reported to the IRB during the course of the study and prior to the next continuing review?

Certain information must be reported to the IRB in a prompt manner, within FIVE (5) business days of the investigator becoming aware of the information. See "[Reportable New Information Bulletin](#)" for a list of information that is requires prompt reporting.

All other events can be reported to the IRB in an aggregate fashion at the time of continuing review.

How do I submit a protocol modification?

Complete the “Create Modification” application in CICERO. Attach relevant documents and submit. Please note that research must continue to be conducted without inclusion of the modification until IRB approval is received.

The IRB must determine if any criteria for approval are affected by the modification and if so, that the particular criterion continues to be met. See “[WORKSHEET: Criteria for Approval and Additional Considerations](#).” For additional information, refer to “[SOP: Pre-Review](#)” and “[CICERO CHECKLIST: Pre-Review and Administrative Review](#).”

How do I submit a continuing review?

Complete the “Create Continuing Review” application in CICERO. Attach relevant documents including any data safety monitoring committee review, and submit. A Continuing Review application must be submitted at least 6 WEEKS PRIOR TO THE EXPIRATION DATE of the IRB approval indicated in the approval letter.

During continuing review the IRB must determine if the criteria for approval continues to be met. See “[WORKSHEET: Criteria for Approval and Additional Considerations](#).” For additional information, refer to “[SOP: Pre-Review](#)” and “[CICERO CHECKLIST: Pre-Review and Administrative Review](#).”

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

What do I do if my study expires?

If the IRB approval for your study expires, all Human Research procedures related to the protocol under review must cease, including recruitment, advertisement, screening, enrollment, consenting, interventions, interactions, and collection of research data. In addition, any data analyses of previously collected research data must cease. Continuing Human Research procedures without IRB approval is a violation of federal regulations.

If current participants 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 participants. If current participants will be harmed by stopping human research procedures that are not available outside the human research context, immediately contact the IRB chair for guidance. Remember that research data cannot be collected during study expiration.

How do I close out a study?

To be eligible for closure, the IRB study must meet all of the following criteria:

- Data collection is complete;
- There is no more participant contact, including phone calls, long term follow up, data collection visits, and surveys;

- The only research activity being conducted is data analysis of de-identified data.

Complete the “Closure Report” in CICERO. Attach relevant documents and submit the report. A Closure Report must be submitted within 45 days of study closure. If you fail to submit a Closure Report to close out Human Research, you will be restricted from submitting new Human Research until the completed application has been received.

If the Closure Report for closing out a Human Research study is not received by the date requested in the approval letter, you will be restricted from submitting new Human Research until the completed application is received.

What does it mean to be on the “restricted list”?

If your IRB approval lapses for any reason, your new research applications will not be reviewed by the IRB. Also, if you fail to submit a protocol continuing review by the date requested on the approval letter or you fail to submit a protocol closure report within 45 days of the end of the study, your new research applications will not be reviewed by the IRB. You will know you are on the restricted list if your name appears in red on any of your research protocols in CICERO.

Once you have submitted the outstanding continuing review or protocol closure report, your name will be taken off the restricted list.

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.

If your research is regulated by the FDA, refer to [Appendix A](#) for specific research record retention guidelines.

If your research involves the VA, refer to [Appendix A](#) for specific research record retention guidelines.

What happens if I leave UMB?

If you are planning to move to another location and leave UMB, the IRB must be notified. You can either have another UMB investigator assume Principal Investigator responsibilities, or you can close each of your research studies with the IRB, or you can transfer the research studies to the new location.

You must also notify the IRB in writing of the plan for either destroying the data or transferring the data to another Principal Investigator. The original research study documents are the property of UMB and must remain at UMB.

What if I need to use an unapproved drug or device in a life-threatening situation and there is no time for prior IRB review?

Contact the Human Research Protections Office (HRPO) or IRB chair immediately to discuss the situation. If there is no time to make this contact, see the “[WORKSHEET: Emergency Use of a Test Article in a Life Threatening Situation](#)” for the regulatory criteria allowing such a use and make sure these criteria are followed. You will need to submit a report of the use to the IRB WITHIN FIVE DAYS of the use and an IRB application for initial review WITHIN 30 DAYS.

If you fail to submit the report within five days or the IRB application for initial review within 30 days, you will be restricted from submitting new Human Research until the report and IRB application for initial review have been received. For additional information, see “[SOP: Emergency Use of a Test Article](#)”

Emergency use of an unapproved drug or biologic in a life-threatening situation without prior IRB review is “research” as defined by FDA, the individual getting the test article is a “subject” as defined by FDA, and therefore is governed by FDA regulations for IRB review and informed consent. Emergency use of an unapproved device in a life-threatening situation 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 or device in a life-threatening situation without prior IRB review cannot be considered a “subject” as defined by DHHS and their results cannot be included in prospective “research” as that term is defined by DHHS.

How do I perform research in an emergency setting when consent cannot be obtained prior to the research procedures?

Please see “[CICERO CHECKLIST: Waiver or Alteration of the Consent Process.](#)” for the criteria that IRB needs to determine are met to approve the conduct of such research.

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 on the HRPO website at <http://umaryland.edu/hrp>.

If you have any questions or concerns, about the Human Research Protection Program, contact the Human Research Protections Office (HRPO) at:

Human Research Protections Office
620 W. Lexington Street, Second Floor
Baltimore, Maryland 21201
hrpo@umaryland.edu
(410) 706-5037



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 Human Research Protections Office (HRPO), follow the directions in the “[HUMAN RESEARCH PROTECTION PROGRAM PLAN](#)” under “Reporting and Management of Concerns.”

Appendix A-1 Additional Requirements for DHHS-Regulated Research¹

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 that data includes 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 participants, investigators should explain whether already collected data about the participants will be retained and analyzed even if the participants choose to withdraw from the research.

¹ <http://www.hhs.gov/ohrp/policy/subjectwithdrawal.html>

Appendix A-2 Additional Requirements for FDA-Regulated Research

1. When a subject withdraws from a study:²
 - a. The data collected on the subject 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:³
 - 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

² <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126489.pdf>

³ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.7>

- 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 participants 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 participants.
 - g. Follow FDA requirements for inspection of investigator's records and reports⁹
 - 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 substances¹⁰
 - 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.¹¹
 - 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 participants 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 investigators¹²
 - i. Awaiting approval: An investigator may determine whether potential participants would be interested in participating in an investigation, but must not request the written informed consent of

⁹ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.68>

¹⁰ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.69>

¹¹ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.100>

¹² <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.110>



- 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 participants 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:¹³
- 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:

¹³ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=812.140>

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. Inspections¹⁴
- 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 participants: An investigator must permit authorized FDA employees to inspect and copy records that identify participants, 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

¹⁴ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=812.145>

have not been submitted or are incomplete, inaccurate, false, or misleading.

- e. Prepare and submit the following complete, accurate, and timely reports¹⁵
- 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 and the IRB 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 participants, FDA approval 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.
 - 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.

¹⁵ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.150>

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

1. Investigator's Qualifications and Agreements
 - 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 through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB, and/or the regulatory authorities.
 - b. The investigator should be thoroughly familiar with the appropriate use of the investigational product, as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.
 - c. The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.
 - d. The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authorities.
 - e. The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.
2. Adequate Resources
 - a. The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable participants within the agreed recruitment period.
 - b. The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.
 - c. The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
 - d. The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product, and their trial-related duties and functions.
3. Medical Care of Trial Participants
 - a. A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.
 - b. During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illnesses of which the investigator becomes aware.
 - c. It is recommended that the investigator inform the subject's primary physician

about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

- d. Although a subject is not obliged to give his/her reasons for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reasons, while fully respecting the subject's rights.

4. Communication with IRB

- a. Before initiating a trial, the investigator/institution should have written and dated approval opinion from the IRB for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to participants.
- b. As part of the investigator's/institution's written application to the IRB, the investigator/institution should provide the IRB with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB.
- c. During the trial the investigator/institution should provide to the IRB all documents subject to review.

5. Compliance with Protocol

- a. The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authorities and which was given approval opinion by the IRB. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.
- b. The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval opinion from the IRB of an amendment, except where necessary to eliminate an immediate hazards to trial participants, or when the changes involves only logistical or administrative aspects of the trial (e.g., change in monitors, change of telephone numbers).
- c. The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.
- d. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to trial participants without prior IRB approval opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendments should be submitted: a) to the IRB for review and approval opinion, b) to the sponsor for agreement and, if required, c) to the regulatory authorities.

6. Investigational Product

- a. Responsibility for investigational product accountability at the trial site rests with the investigator/institution.
- b. Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product

accountability at the trial site to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution..

- c. The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product. These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product and trial participants. Investigators should maintain records that document adequately that the participants were provided the doses specified by the protocol and reconcile all investigational product received from the sponsor.
- d. The investigational product should be stored as specified by the sponsor and in accordance with applicable regulatory requirements.
- e. The investigator should ensure that the investigational product are used only in accordance with the approved protocol.
- f. The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.
- g. Randomization Procedures and Unblinding: The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product.

7. Informed Consent of Trial Participants

- a. In obtaining and documenting informed consent, 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. Prior to the beginning of the trial, the investigator should have the IRB's written approval opinion of the written informed consent form and any other written information to be provided to participants.
- b. The written informed consent form and any other written information to be provided to participants should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB's approval opinion in advance of use. The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.
- c. Neither the investigator, nor the trial staff, should coerce or unduly influence a



- subject to participate or to continue to participate in a trial.
- d. None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally authorized representative 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 agents from liability for negligence.
 - e. The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally authorized representative, of all pertinent aspects of the trial including the written information and the approval opinion by the IRB.
 - f. The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally authorized representative and the impartial witness, where applicable.
 - g. Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally authorized representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally authorized representative.
 - h. Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally authorized representative, and by the person who conducted the informed consent discussion.
 - i. If a subject is unable to read or if a legally authorized representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to participants, is read and explained to the subject or the subject's legally authorized representative, and after the subject or the subject's legally authorized representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally authorized representative, and that informed consent was freely given by the subject or the subject's legally authorized representative.
 - j. Both the informed consent discussion and the written informed consent form and any other written information to be provided to participants should include explanations of the following:
 - i. That the trial involves research.
 - ii. The purpose of the trial.

- iii. The trial treatments and the probability for random assignment to each treatment.
- iv. The trial procedures to be followed, including all invasive procedures.
- v. The subject's responsibilities.
- vi. Those aspects of the trial that are experimental.
- vii. The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
- viii. The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- ix. The alternative procedures or courses of treatment that may be available to the subject, and their important potential benefits and risks.
- x. The compensation and/or treatment available to the subject in the event of trial related injury.
- xi. The anticipated prorated payment, if any, to the subject for participating in the trial.
- xii. The anticipated expenses, if any, to the subject for participating in the trial.
- xiii. That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
- xiv. That the monitors, the auditors, the IRB, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally authorized representative is authorizing such access.
- xv. That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
- xvi. That the subject or the subject's legally authorized representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
- xvii. The persons to contact for further information regarding the trial and the rights of trial participants, and whom to contact in the event of trial-related injury.
- xviii. The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
- xix. The expected duration of the subject's participation in the trial.
- xx.

The approximate number of participants involved in the trial.

- k. Prior to participation in the trial, the subject or the subject's legally authorized representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the participants. During a subject's participation in the trial, the subject or the subject's legally authorized representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to participants.
 - l. When a clinical trial (therapeutic or non-therapeutic) includes participants who can only be enrolled in the trial with the consent of the subject's legally authorized representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.
 - m. Except as described in 4.8.14, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in participants who personally give consent and who sign and date the written informed consent form.
 - n. Non-therapeutic trials may be conducted in participants with consent of a legally authorized representative provided the following conditions are fulfilled: a) The objectives of the trial cannot be met by means of a trial in participants who can give informed consent personally. b) The foreseeable risks to the participants are low. c) The negative impact on the subject's well-being is minimized and low. d) The trial is not prohibited by law. e) The approval opinion of the IRB is expressly sought on the inclusion of such participants, and the written approval opinion covers this aspect. Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Participants in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.
 - o. In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally authorized representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally authorized representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval opinion by the IRB, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally authorized representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested.
8. Records and Reports
- a. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

- b. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.
 - c. Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections. Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.
 - d. The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirements. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.
 - e. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.
 - f. The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.
 - g. Upon request of the monitor, auditor, IRB, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.
9. Progress Reports
- a. The investigator should submit written summaries of the trial status to the IRB annually, or more frequently, if requested by the IRB.
 - b. The investigator should promptly provide written reports to the sponsor, the IRB and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to participants.
10. Safety Reporting
- a. All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify participants by unique code numbers assigned to the trial participants rather than by the participants' names, personal identification numbers, and/or addresses. The investigator should also comply

with the applicable regulatory requirements related to the reporting of unexpected serious adverse drug reactions to the regulatory authorities and the IRB.

- b. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.
 - c. For reported deaths, the investigator should supply the sponsor and the IRB with any additional requested information (e.g., autopsy reports and terminal medical reports).
 - d. **Premature Termination or Suspension of a Trial** If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial participants, should assure appropriate therapy and follow-up for the participants, and, where required by the applicable regulatory requirements, should inform the regulatory authorities. In addition:
 - i. If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB, and should provide the sponsor and the IRB a detailed written explanation of the termination or suspension.
 - ii. If the sponsor terminates or suspends a trial, the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB and provide the IRB a detailed written explanation of the termination or suspension.
 - iii. If the IRB terminates or suspends its approval opinion of a trial, the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.
11. **Final Reports by Investigator:** 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 the regulatory authorities with any reports required.



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 Department of Defense approval. Consult with the Department of Defense funding component to see whether this is a requirement.
2. Department of Defense employees (including 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 Department of Defense cannot be paid for conducting research while on active duty.
3. Department of Defense components might have stricter requirements for research-related injury than the DHHS regulations.
4. There may be specific Department of Defense educational requirements or certification required.
5. When conducting multi-site research, a formal agreement between organizations is required to specify the roles and responsibilities of each party.
6. Other specific requirements of Department of Defense (DOD) research be found in the “Additional Criterion for Department of Defense (DOD) Research” section in the IRB’s [“WORKSHEET: Criteria for Approval and Additional Considerations.”](#)

Additional Requirements for Department of Navy (DON) Research

1. Surveys usually require Department of Navy review and approval. See SECNAVINST 5300.8B for more information.
2. Other specific requirements of Department of Navy (DON) research be found in the “Additional Criterion for Department of Navy (DON) Research” section in the IRB’s [“WORKSHEET: Criteria for Approval and Additional Considerations.”](#)

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

1. Research that involves one or more of the following is considered by DOE to be human subjects research and requires IRB review:
 - a. Intentional modification of the human environment
 - b. Study of human environments that use tracer chemicals, particles or other materials to characterize airflow.
 - c. Study in occupied homes or offices that:
 - i. Manipulate the environment to achieve research aims.
 - ii. Test new materials.
 - iii. 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.
2. You must complete and submit to the IRB the DOE "Checklist for IRBs to Use in Verifying that HS Research Protocols are In Compliance with DOE Requirements" (http://human.subjects.energy.gov/other-resources/documents/IRB-template-for-reviewing-PII-protocols-2010_ac.pdf) if your research includes Personally Identifiable Information. Please indicate with each item in the checklist where this is addressed within the protocol you have submitted to the IRB for review.
3. You must report the following within ten business days to the Department of Energy human subjects research program manager:
 - a. Any significant adverse events, unanticipated risks; and complaints about the research, with a description of any corrective actions taken or to be taken
 - b. Any suspension or termination of IRB approval of research
 - c. Any significant non-compliance with HRPP procedures or other requirements.
4. You must report the following within three business days to the Department of Energy human subject research program manager.
 - a. Any compromise of personally identifiable information must be reported immediately.
5. Research involving human participants also includes studies of the intentional modification of the human environment; generalizable includes the study of tracer chemicals, particles or other materials to characterize airflow.
6. Generalizable also includes studies in occupied home or offices that:
 - a. Manipulate the environment to achieve research aim;
 - b. Test new materials;
 - c. Involve collecting information on occupants' views of appliances, materials; or
 - d. Devices installed in their homes or their energy-saving behaviors through surveys and focus groups.

Generalizable should be viewed in terms of the contribution to knowledge with the specific field of study.
7. Other specific requirements of the Department of Energy (DOE) research can be found in the "Additional Requirements for Department of Energy (DOE) Research" section in the IRB's "[WORKSHEET: Additional Federal Criteria \(HRP-311\)](#)."



Appendix A-6 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 children¹⁶ involved in the research¹⁷ 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 Department of Education (ED) Research can be found in the “Additional Criterion for Department of Education (ED) Research” section in the IRB’s [“WORKSHEET: Criteria for Approval and Additional Considerations.”](#)

¹⁶ 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.

¹⁷ 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.

Appendix A-7 Additional Requirements for Veterans Administration (VA) Research

- 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 principle 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 and VHA Directive 2012-030, Credentialing of Health Care Professionals, or successor policy). 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 Web site at: <http://www.research.va.gov/pride/training/options.cfm>. All other applicable VA and VHA training requirements at the local and national level must be met (e.g., privacy and information security training).
- 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 from 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.

- 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 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 a research repository from a previous study is used to identify 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 are 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 PO 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.
- 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, and
 - The person obtaining the informed consent (unless the signature is waived by the IRB)
- 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 as is typical or that the software provides the current date when signed.
-
- **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.
- **Reporting.** The investigator is responsible for reporting within 5 business days unanticipated problems involving risks to subjects or others, serious unanticipated problems involving risks to subjects or others, local unanticipated serious adverse events, 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 Handbook 1058.01. This requirement is in addition to other applicable reporting requirements (e.g., reporting to the sponsor under FDA requirements.) The unfounded classification of a serious adverse event as "anticipated" constitutes serious non-compliance.
- **Research Records.** All written information given to subjects must be in the investigator's research file along with the consent form(s). The investigator's research records are not yet scheduled in VHA 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 are admitted to VA medical facilities as in-patients, treated as outpatients at VA medical facilities, or when research procedures or interventions are 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) (see VHA Handbook 1907.01). Informed consent documents are not required to be in the health record.
- **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 Handbook 1200.05, 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 Handbook 1200.01);
 - An IRB approval letter;

- A copy of the approved study protocol;
- A copy of VA Form 10-9012, when appropriate;
- An IB, when appropriate;
- Any sponsor-provided documents relating to the storage, preparation, dispensing, and accountability of the investigation products;
- 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 if clinical investigation is suspended or terminated by the IRB, R&D Committee, FDA, or other oversight group (e.g., ORO or the study sponsor); and
- Notice of when the study is 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 (herbals, nutraceuticals).
- The PI or LSI must place the completed VA Form 10-9012, or electronic equivalent, in the subject's medical record.
- 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. 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 Handbook 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:
- Other specific requirements of Veterans Administration (VA) research be found in the “Additional Requirements for Veterans Administration (VA) Research” section in the IRB’s “[WORKSHEET: Additional Federal Criteria \(HRP-311\)](#).”
- Vulnerable Subjects
 - The following populations are considered categorically vulnerable and have specific VA requirements for their inclusion in research:
 - Fetuses. Research in which the focus is either a fetus, or human fetal tissue, *in-utero* or *ex-utero* (or uses human fetal tissue), must not be conducted by VA investigators while on official duty, or at VA facilities, or at VA approved off-site facilities.
 - Neonates. Interventional research enrolling neonates can not be conducted by VA investigators while on official duty, or at VA facilities, or at VA approved off-site facilities. Prospective observational and retrospective record review studies that involve neonates or neonatal outcomes are permitted.
 - 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.
- 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.
 - If such a waiver is granted, the research must comply with the requirements of 45 CFR 465.301 - 46.306.
- Research Involving Children
 - Research involving children must not be 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 an VA research involving children and must comply with the requirements of 45 CFR 46.401 - 46.404 and 46.408.
- 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
 - For studies that do not involve a medical intervention (e.g., observational studies, including interview and questionnaire studies), no annotation may be made in the health record.
 - For studies that involve a medical intervention, a progress note entry should indicate that an individual has been enrolled in a research study, any details that would affect the subject's clinical care, and the name and contact information for the investigator conducting the study.

Subjects' informed consent forms and HIPAA authorization documents are not to be included in the health record.

- Investigators should work with the research office in their facility to assure that when Veterans are enrolled in a study protected by a Certificate of Confidentiality, 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 Handbook 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 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, ships, or 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 preparatory to research activities without appropriate VA approvals (see VHA Handbook 1605.1).
- During the preparatory to research 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 ends when the protocol is submitted to the IRB.
- Participation Of Non-Veterans As Research Subjects
 - Non-Veterans may be entered into a VA-approved research study that involves VA outpatient or VA hospital treatment (38 CFR 17.45, 17.92), but only when there are insufficient Veteran patients suitable for the study. The investigator must justify including non-Veterans and the IRB must review the justification and provide specific approval for recruitment of non-Veterans.
 - Outpatient Care for Research Purposes. Any person who is a bona fide volunteer may be furnished outpatient treatment when the treatment to be rendered is part of an approved VA research study and there are insufficient Veteran patients suitable for the study (38 CFR §17.92).
 - Hospital Care for Research Purposes. Any person who is a bona fide volunteer may be admitted to a VA hospital when the treatment to be rendered is part of an approved VA research study and there are insufficient Veteran patients suitable for the study (38 CFR §17.45).
 - Non-Veterans may be recruited for studies that will generally benefit Veterans and their well-being but would not include Veterans as subjects. Examples include surveys of VA providers, studies involving Veterans’ family members, or studies including active duty military personnel. Although active duty military personnel are not considered Veterans, they should be included in VA studies whenever appropriate.
 - In addition to the non-Veterans referenced above, active duty military personnel may be entered into VA research conducted jointly by VA and DoD or within DoD facilities.
 - All VA regulations and policies related to Veterans as research subjects apply to non-Veterans entered into VA research.
 - Non-Veterans may not be entered into VA studies simply because a non-Veteran population is easily accessible to the investigator.



- Investigators must follow VHA Handbook 1605.04, Notice of Privacy Practices, to provide notice of privacy practices and acknowledgement for any non-Veteran enrolled in the approved protocol.
- Student and Other Trainee Research at Veterans Administration (VA) Facilities
 - Trainees (e.g., students, residents, or fellows of any profession) may serve as participants, but not PIs within a VA facility, use VA human subjects data, or use human biological specimens that have been collected within VA for clinical, administrative, or research purposes only when The study has been approved by the local VA medical facility and IRB, if appropriate; and
 - Either they are:
 - Enrolled in an institution with an educational affiliation agreement with that VA facility; or
 - Directly appointed to a VA training program that has not external institutional sponsorship (e.g., VA Advanced Fellowship). NOTE: A waiver may be obtained from the CRADO under special circumstances.
 - A VA investigator sufficiently experienced in the area of the trainee's research interest must serve as PI and is responsible for oversight of the research and the trainee/student. The PI is responsible for ensuring the trainee/student complies with all applicable local, VA and other Federal requirements including those related to research, information security, and privacy.
 - If the trainee does not complete all aspects of the research prior to leaving VA, the investigator must ensure the protocol is completed or terminated in an orderly fashion, and in accordance with all applicable local, VA, and other Federal requirements.
 - When the trainee leaves VA, the VA investigator is responsible for ensuring that all research records are retained by the VA.
- Other specific requirements of Veterans Administration (VA) research be found in the “Additional Requirements for Veterans Administration (VA) Research” section in the IRB’s “[WORKSHEET: Additional Federal Criteria \(HRP-311\)](#).”

Appendix A-8 Additional Requirements for Department of Justice (DOJ) Research

Additional Requirements for the Department of Justice (DOJ) Research conducted within the Federal Bureau of Prisons

1. The project must not involve medical experimentation, cosmetic research, or pharmaceutical testing.
2. The research design must be compatible with both the operation of prison facilities and protection of human subjects.
3. Investigators must observe the rules of the institution or office in which the research is conducted.
4. 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.
5. The research must be reviewed and approved by the Bureau Research Review Board.
6. 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: No longer in Bureau of Prisons custody. Participating in authorized research being conducted by Bureau employees or contractors.
7. A non-employee of the Bureau may receive records in a form not individually identifiable when advance adequate written assurance that the record will be used solely as a statistical research or reporting record is provided to the agency.
8. 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.
9. 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.
10. 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.

11. 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, a 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.
12. You must have academic preparation or experience in the area of study of the proposed research.
13. 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.
14. The IRB application must include a comprehensive statement, which 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: Ensure the security of any individually identifiable data that are being collected for the study.
 - h. Destroy research records or remove individual identifiers from those records when the research has been completed.

- i. Description of any anticipated effects of the research study on organizational programs and operations.
 - j. Relevant research materials such as vitae, endorsements, sample consent statements, questionnaires, and interview schedules.
15. The IRB application includes a statement regarding assurances and certification required by federal regulations, if applicable.
16. You must assume responsibility for actions of any person engaged to participate in the research project as an associate, assistant, or subcontractor.
17. At least once a year, you must provide the Chief, Office of Research and Evaluation, with a report on the progress of the research.
18. 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.
19. You must include an abstract in the report of findings.
20. In any publication of results, the investigator shall acknowledge the Bureau's participation in the research project.
21. You must expressly disclaim approval or endorsement of the published material as an expression of the policies or views of the Bureau.
22. 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.

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

1. The projects 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.