



University of Maryland, Baltimore

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 to all research, unless exempt, regardless of the sponsor or funding source.

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 School of Medicine and reports to the Institutional Official. Refer to “HUMAN RESEARCH PROTECTION PROGRAM PLAN.” You can access the HRPO website via www.hrpo.umaryland.edu.



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.umd.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: Susan C. Buskirk, MS
Title: Assistant Dean, Human Research Integrity and Compliance
Dean’s Office, Human Research Protections Office
800 W. Baltimore Street, Suite 100
Baltimore, Maryland 21201
Email: sbuskirk@som.umaryland.edu
(410) 706-4937

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.

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 HRPO website at www.hrpo.umaryland.edu.

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 two-year period, after which time a refresher CITI course must be completed. A minimum score of 85% 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://medschool.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:
www.umaryland.edu/cct
- If your research is sponsored by a commercial sponsor, please refer to the Corporate Contracts section of the CCT website:
www.umaryland.edu/cct/Corporate%20Contracts.html
- 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://research.umaryland.edu/>
- 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. “UMB HRPP SOP: IRB Fees for Industry-Supported Applications.”

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@som.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 investigators is responsible for ensuring that all investigators and research staff comply with this requirement.

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

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 can reference pages in the sponsor's protocol in the corresponding sections of the CICERO application. If you create your own separate research protocol, it is called an "Investigator Protocol". You will find a template on the HRPO website, www.hrpo.umaryland.edu, in the Investigator Toolkit under the Worksheets and Checklists section.

Here are some key points to remember when completing the CICERO application or for 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. 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.”

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. See “UMB HRPP SOP: Required Registration with ClinicalTrials.gov.”

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, 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?](#)”
- 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 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 IRB analyst for your study. You can 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. 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.
- 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.
 - Assure that each participant is adequately informed and freely consents to participate 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 policies 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.
- 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 and for all Veterans Administration (VA) research 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 is to be provided to the subject.
- 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” for a list of information that requires prompt reporting.

Protocol exception (PE) requests must be submitted AND RECEIVE IRB APPROVAL PRIOR to implementing the proposed deviation.

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 and complete a protocol exception request. 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 “CICERO CHECKLIST: 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 device 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.



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 www.hrpo.umaryland.edu.

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

Julie Doherty, MSN
Director, Regulatory Operations
Human Research Protections Office
800 W. Baltimore Street, Suite 100
Baltimore, Maryland 21201
jdoherty@som.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 for a use for which it is under investigation and to preclude

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>



- commercialization of the drug before it is approved for commercial distribution.
- iii. An investigator must not commercially distribute or test market an investigational new drug.
- b. Follow FDA requirements for general responsibilities of investigators⁴
 - i. An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of participants under the investigator's care; and for the control of drugs under investigation.
 - ii. An investigator must, in accordance with the provisions of 21 CFR §50, obtain the informed consent of each human subject to whom the drug is administered, except as provided in 21 CFR §50.23 or §50.24 of this chapter.
 - iii. Additional specific responsibilities of clinical investigators are set forth in this part and in 21 CFR §50 and 21 CFR §56.
 - c. Follow FDA requirements for control of the investigational drug⁵
 - i. An investigator must administer the drug only to participants under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator.
 - ii. The investigator must not supply the investigational drug to any person not authorized under this part to receive it.
 - d. Follow FDA requirements for investigator recordkeeping and record retention⁶
 - i. Disposition of drug:
 - 1. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by participants.
 - 2. If the investigation is terminated, suspended, discontinued, or completed, the investigator must return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 21 CFR §312.59.
 - ii. Case histories.
 - 1. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation.
 - 2. Case histories include the case report forms and supporting data including, for example, signed and dated consent

⁴ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.60>

⁵ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.61>

⁶ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.62>



- forms and medical records including, for example, progress notes of the physician, the individual's hospital charts, and the nurses' notes. The case history for each individual must document that informed consent was obtained prior to participation in the study.
- iii. Record retention: An investigator must retain required records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.
- e. Follow FDA requirements for investigator reports⁷
- i. Progress reports: The investigator must furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained.
 - ii. Safety reports: An investigator must promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator must report the adverse effect immediately.
 - iii. Final report: An investigator must provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation.
 - iv. Financial disclosure reports:
 - 1. The clinical investigator must provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under 21 CFR §54.
 - 2. The clinical investigator must promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.
- f. Follow FDA requirements for assurance of IRB review⁸
- i. An investigator must assure that an IRB that complies with the requirements set forth in 21 CFR §56 will be responsible for the initial and continuing review and approval of the proposed clinical study.
 - ii. The investigator must also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human 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.

⁷ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.64>

⁸ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.66>



- 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 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

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

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

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

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



- 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:
 - 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

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



- 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 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.

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

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



- 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.



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. 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. You must report the following within ten business days to the Department of Energy human subject 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.
2. 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.
3. Other specific requirements of Department of Energy (DOE) research be found in the “Additional Criterion for Department of Energy (DOE) Research” section in the IRB’s “WORKSHEET: Criteria for Approval and Additional Considerations.”



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

- Flag the medical record when required by the IRB.
- To receive an investigational drug, you must:
 - Provide the Pharmacy Service or Research Investigational Pharmacy information on each subject receiving an investigational drug through the electronic medical record or other locally approved means. 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, i.e., herbals, nutraceuticals.
 - Ensure the local Pharmacy Service or Research Service Investigational Pharmacy receives:
 - Documentation of IRB and any other relevant approvals.
 - A copy of VA Form 10-9012, Investigational Drug Information Record, when applicable.
 - A copy of the current approved protocol.
 - A copy of the informed consent form for each participating subject with all appropriate signatures.
 - Documentation of the IRB continuing review approval.
 - Copies of sponsor-related correspondence specific to the drug(s) as appropriate.
 - Copies of all correspondence addressed to the investigator from the FDA (and other involved authorities) specific to the investigational drug(s) as appropriate.
 - Inform the Chief of the Pharmacy Service, the research pharmacy when applicable, and the IRB in writing when a study involving investigational drugs has been suspended, terminated, or closed.
 - Comply with all dispensing requirements.
 - Comply with all documentation requirements and make relevant records accessible to the investigational drug pharmacist when requested.
 - Comply with all VHA pharmacy requirements regarding receiving, dispensing, storing, and record-keeping for investigational drugs.
 - Inform the pharmacy service of the IRB's and Research and Development Committee's approval through Form 10-1223.
 - Provide the pharmacy with a signed copy of Form 10-1086 to document each subject's consent to participate in the study.
 - Inform the Chief, Pharmacy Service, and the Research and Development Committee when a study involving investigational drugs had been terminated.
 - Maintain a record of the research in the subject's medical chart.
 - Maintain signed and dated consent documents for five years after completion of the research.
- Follow this organization's procedures to ensure reporting in writing to the IRB within 5 business days of becoming aware of unanticipated problems involving



risks to subjects or others, apparent serious or continuing non-compliance, suspension of IRB approval, termination of IRB approval, and local (i.e., occurring in the reporting individual's own VA facility) unanticipated serious adverse events in writing to the IRB within five business days of. 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.

- The principal investigator, local site investigator, and investigator must uphold professional and ethical standards and practices and adhere to all applicable VA and other Federal requirements, including the local VA facility's SOPs, regarding the conduct of research and the protection of human subjects.
- 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
 - Disclosing Conflicts of Interests. This means disclosing to the IRB any potential, actual, or perceived conflict of interest of a financial, professional, or personal nature that may affect any aspect of the research, and complying with all applicable VA and other Federal requirements regarding conflict of interest.
 - Ensuring Adequate Resources. This means ensuring there are adequate resources to carry out the research safely. This includes, but is not limited to, sufficient investigator time, appropriately qualified research team members, equipment, and space.
 - Ensuring Qualified Research Staff. This means ensuring research staff are qualified (e.g., including but not limited to appropriate training, education, expertise, credentials and, when relevant, privileges) to perform procedures assigned to them during the study. In a protocol, study team members are generally identified by name or by title.
 - If a study team member is identified by name in the IRB-approved protocol, a replacement or termination of their role constitutes a change in the protocol. Such a change requires IRB approval (e.g., if an IRB-approved protocol specifically identified the name of a medical monitor and later another individual was identified to replace the medical monitor, the protocol would require an amendment reflecting the change in the name of the medical monitor. This protocol change would require IRB approval prior to initiation of the change, unless it was necessary to eliminate apparent immediate hazards to the subjects).
 - If a study team member is replaced by another individual and the IRB-approved protocol identifies the person by title and not name, a replacement by another individual with the same title is not a protocol change. No IRB approval is required (e.g., if a principle investigator appointed a new research study coordinator to replace the original research study coordinator in an IRB-approved protocol when neither is mentioned



by name, the replacement in personnel does not require approval by IRB because the protocol remains unchanged).

- IRB may also require a specific individual(s) by name to be part of the study team as a condition for IRB approval of the research. In that case, a proposed change in that specific individual would require IRB approval.
- Promptly Reporting Changes in principle investigator or local site investigator. This means promptly reporting any changes in the principle investigator or local site investigator to the IRB. Changes in other key research staff, if any, must be reported at time of continuing review, or sooner as required by local SOPs. These changes include, but are not limited to, additions to or loss of staff. Changes in the principle investigator, local site investigator, Co-principle investigator, or Co-local site investigator of an IRB-approved project must be evaluated and approved by IRB to ensure the new individual meets the criteria described in 38 CFR 16.111.
- Overseeing the Research Staff. This means overseeing and being responsible for ensuring the research staff under the investigator's direction comply with all applicable requirements including, but not limited to, implementing the research study in accordance with the approved protocol.
- Ensuring Complete Information in Research Protocol. This means ensuring the research protocol contains all required information.
- Obtaining Written Approvals. This means obtaining written approval(s) before initiating research. Before initiating the research study at a given site, IRB approval must be obtained in writing from the Chair or other voting member of the IRB, and all other committees (e.g., R&D Committee), subcommittees, and other approvals according to applicable local, VA, and other Federal requirements.
 - For a VA multi-site study, not only the principle investigator, but also all local site investigators, must obtain such approvals from the relevant local VA facilities' IRBs of record and all other local committees, subcommittees, and other approvals according to the respective applicable local, VA and other Federal requirements.
 - Research cannot be initiated at any given site until the local investigator has obtained written notification that the research can be initiated from the local ACOS for R&D.
- Implementing the Study as Approved. This means ensuring the study is implemented as approved by the IRB and in accordance with other required approvals and with all applicable local, VA, and other Federal requirements including, when applicable, those for research involving investigational drugs or investigational devices.
- Maintaining Investigator's Research Records. This means maintaining written documentation on file that the protocol is being implemented as approved by IRB and in accordance with other required approvals.



- Retain research records until disposition instructions are approved by the National Archives and Records Administration and are published in VHA's Records Control Schedule (RCS 10-1).
- Research records include the following when relevant to the study:
 - Copies of all IRB-approved versions of the protocol and amendments.
 - Case report forms and supporting data, including, but not limited to, signed and dated informed consent forms and HIPAA authorizations.
 - Documentation on each subject including, but not limited to:
 - Informed consent,
 - Interactions with subjects by telephone or in person,
 - Observations,
 - Interventions, and
 - Other data relevant to the research study, including, but not limited to:
 - Progress notes,
 - Research study forms,
 - Surveys, and
 - Questionnaires.
 - Reports of adverse events.
 - Data analyses.
 - Reports including, but not limited to, abstracts and other publications.
 - All correspondence including, but not limited to, that with the funding source or sponsor, and with applicable oversight entities including, but not limited to, IRB, R&D Committee, ORO, and FDA.
 - A master list of all subjects for whom informed consent has been obtained in the study.
- Documents must be maintained so that they may be audited by the facility RCO or other entities according to applicable sponsor, local, VA and other Federal requirements, and
- An Accounting of Disclosure must be maintained for each and every disclosure of information from this study to a non-VA entity. NOTE: The facility Privacy Officer can assist in providing a mechanism to account for this disclosure.
- Obtaining Informed Consent. This means ensuring that no human being is involved as a subject in research covered by this Handbook unless legally effective informed consent of the subject or the subject's legally authorized representative has been obtained (38 CFR 16.116). The informed consent must be obtained and documented 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). The only exceptions are if the IRB of record determines the research is exempt, or approves a waiver of informed consent, or approves a waiver of the signed informed consent form.
 - Designating Responsibility for Obtaining Informed Consent. If the principle investigator or local site investigator does not personally obtain informed consent, the investigator must formally and prospectively designate to another



research team member in writing the protocol or the application for IRB approval the responsibility for obtaining informed consent, whether or not a waiver of documentation of informed consent has been approved by the IRB. This designee must be a member of the research team.

- Any person designated to obtain informed consent must receive appropriate training and be knowledgeable enough about the protocol to answer the questions of prospective subjects.
- The principle investigator or local site investigator does not have to designate the individual by name, but can designate the position(s) title in the protocol or the application for IRB approval.
- Version of Informed Consent Form. The most current IRB-approved version of VA Form 10-1086, Research Consent Form, for each study (or the most current IRB-approved electronic version of VA Form 10-1086) must be used as the informed consent form.
- Circumstances Under Which Informed Consent is Obtained. The investigator, or designee, must seek informed consent only under circumstances that:
 - Provide the prospective subject or legally authorized representative sufficient opportunity to consider whether or not to participate, and
 - Minimize the possibility of coercion or undue influence.
- Usual Care. The investigator, or designee, must ensure the Informed Consent process clearly defines for the subject which potential risks are related to the research and, therefore, must be discussed with the research team, versus those associated solely with usual care provided by the subject's health care provider. The informed consent process must include language advising subjects to review the risks of the latter with their health care providers.
- Documentation of Informed Consent
 - When documentation of informed consent is not waived by IRB, the investigator or designee must ensure the documentation is in accordance with paragraph 33 of this Handbook and includes:
 - The signature and date of the subject or the subject's legally authorized representative, and
 - The signature and date of the person obtaining the informed consent, and
 - The signature of the witness and the date of the subject's or legally authorized representative's signature was witnessed, if required by IRB. (e.g., the IRB may require a witness if the study involves an invasive intervention or an investigational drug or device.) A witness is always required when a short form consent is employed.
 - The witness is required to witness only the subject's or subject's LAR's signature, not the informed consent process (e.g., if the subject does not want the witness to know the nature of the research study), unless the sponsor or IRB requires the witness to witness the informed consent process.



- The witness cannot be the person who obtained informed consent from the subject, but may be another member of the study team or may be a family member.
- If use of facsimile is approved by IRB, the subject may submit the signed and dated informed consent form to the investigator or designee by facsimile.
- Storage of Signed Informed Consent Forms. The investigator must ensure all original signed and dated forms are in the investigator's research files, readily retrievable, and secure.
- Ensuring Consistency of Informed Consent Form, Protocol, and HIPAA Authorization. This means ensuring the language in the informed consent form is consistent with that in the protocol and, when applicable, in the HIPAA authorization.
- Ensuring HIPAA Authorization is Obtained. This means ensuring that no human being is involved as a subject in research covered by this Handbook, unless the investigator or a designee formally and prospectively designated in writing in the protocol by the investigator has obtained legally effective HIPAA authorization for the use and disclosure of the subject's PHI, or has obtained Privacy Board or IRB-approved waiver of HIPAA authorization.
 - If the investigator requires a waiver or alteration of the HIPAA authorization, the investigator must provide the Privacy Board or IRB with information sufficient for the Privacy Board or IRB to find that such waiver or alteration is necessary.
 - Investigators can obtain and use real Social Security numbers only when real Social Security numbers are required to meet the specific aims of the research protocol or to enter information into the subjects' health records. The collection and use of real Social Security numbers must be approved by IRB, and the investigators must follow all applicable VA and other Federal requirements for obtaining and using real Social Security numbers.
- Performing Subject Outreach. This means ensuring that, as part of the local VA facility's Research Subject Outreach Program, the investigator is responsible for:
 - Making every reasonable effort to make available the informational brochure, "Volunteering in Research – Here Are Some Things You Need To Know," (<http://www.research.va.gov/programs/pride/veterans/tri-fold.pdf>) to potential research subjects in settings where investigators may recruit subjects (e.g., clinic waiting areas), and to prospective subjects, and their surrogates where applicable, when the individuals are approached to take part in a study.
 - Ensuring that all informed consent forms provide subjects with required contact information for the VA investigator and relevant study staff. In addition, all informed consent forms must provide a contact independent of the research team in case the research staff cannot be reached, and the subject wish to talk to someone other than the research staff, or the subject wishes to voice concerns or complaints about the research.



- Informing the independent contact person who is independent of the research team (e.g., the facility's patient advocate, a member of the research office staff, or IRB staff) of the relevant details of the study; documenting that this independent contact person has been informed; and ensuring the independent contact person's ability to render proper assistance to potential subjects.
- 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). The initial contact must provide a telephone number or other means that the potential subject can use to verify the study constitutes VA research. 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 VA 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.
- Obtaining IRB Approval for all Changes. This means obtaining IRB approval for all changes to the research protocol (e.g., amendments or modifications), including changes to the IRB informed consent form (the IRB informed consent form is unique to each research study), prior to implementing the changes. The only exception is when it is necessary to change the protocol to eliminate apparent immediate hazards to the subject. The investigator must promptly report these changes to the IRB.
- Submitting Continuing Review Materials. This means ensuring continuing review materials are submitted in a timely manner to provide IRB sufficient time for reviewing and approving the study before IRB approval expires. IRB approval automatically expires if the continuing review and approval does not occur by the expiration date of the current approval.
- Reporting Deviations and Complaints. This means reporting deviations from the protocol and subject complaints to IRB in a time frame specified in local SOPs.
- Reporting Problems and SAEs. This means reporting all unanticipated problems involving risks to subjects or others, and all internal (i.e., local) SAEs, whether related or unrelated to the research, in accordance with local SOPs and VHA Handbook 1058.01.
- Completing Appropriate Actions at Research Project Completion. This means at completion of the research study, completing all required documentation and



- storing research records according to all applicable VA and Federal records retention requirements. If appropriate, the investigator communicates the results to subjects or the community from which subjects were recruited.
- **Transferring of Records.** This means transferring of records by VA upon departure of the investigator. If the investigator leaves VA, all research records are retained by the VA facility where the research was conducted. If the grant is ongoing and the investigator leaves one VA facility to go to another VA facility, the investigator must obtain approval for a copy of relevant materials to be provided to the new VA facility's research office. The approval must be obtained from the first VA facility's research office, any other relevant individuals or offices according to VA and local requirements (e.g., compliance, privacy, or Information Security Officers and the sponsor. The investigator is not the grantee, nor does the investigator own the data.
 - **Maintaining a Master List of All Subjects.** This means the investigator must maintain a master list of all subjects from whom informed consent has been obtained whether or not IRB granted a waiver of documentation of informed consent.
 - Investigators must not add a subject's name to the master list of all subjects until after:
 - Informed consent has been obtained from that subject, and
 - When appropriate, informed consent has been documented using an IRB-approved informed consent form.
 - IRB may waive the requirement for the investigator to maintain a master list for a given study if both of the following conditions are met:
 - There is a waiver of documentation of informed consent, and
 - The IRB determines that including the subjects on such a master list poses a potential risk to the subjects from a breach of confidentiality.
 - If IRB waives the requirement to maintain such a master list, IRB must provide written documentation in the IRB minutes or IRB protocol file justifying the waiver.
 - The investigator must secure the master list appropriately in compliance with all VA confidentiality and information security requirements in the investigator's file for each study.
 - **Ensuring Appropriate Research Laboratory Test Reporting.** This means ensuring research laboratories not report laboratory results that are used for diagnosis, treatment, and prevention of disease in patients, unless the research laboratories are properly accredited and meet all requirements of 42 CFR 493.
 - **Ensuring Requirements of Multi-site Studies**
 - **Ensuring Research is Scientifically Sound.** This means the investigator ensures that the research is scientifically sound.
 - **Ensuring Research Compliance.** This means the investigator ensures that research is in compliance with all applicable local, VA, and other Federal requirements.
 - **Providing a Plan for Recruitment and Selection of Subjects.** The investigator provides a plan for just, fair, and equitable recruitment and selection of subjects.



- The requirement for a plan for just, fair, and equitable recruitment and selection of subjects applies to both prospective and retrospective studies, including studies that use clinical or administrative databases or bio-specimens.
- **Minimizing Risks.** This means the investigator is responsible for minimizing risks to the subjects or others.
 - **Describing Data and Safety Monitoring Plan for Prospective Studies.** This means the investigator describes the data and safety monitoring plan for prospective studies. The data and safety monitoring plan may vary depending on the potential risks, complexity, and nature of the study. The use of an independent DMC needs to be considered if there are multiple clinical sites, the study is blinded, interventions are high-risk, vulnerable populations are included, or when required by the funding organization, FDA, sponsor, or other relevant entity. This plan must include, but is not limited to, the following:
 - What safety information will be collected including SAEs;
 - How the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with subjects);
 - The frequency of data collection including when safety data collection starts;
 - The frequency or periodicity of review of cumulative safety data;
 - If not using a DMC, and if applicable, statistical tests for analyzing the safety data to determine if harm is occurring;
 - Provisions for the oversight of safety data (e.g., by a DMC); and
 - Conditions that trigger an immediate suspension of the research, if applicable.
 - **Describing Data and Safety Monitoring Plan for Retrospective Studies.** This means the investigator describes the safety and monitoring plan for retrospective studies, including studies involving pre-existing data and biological specimens. When applicable, the plan needs to include, but is not limited to, the following:
 - A discussion with the subject of potential study outcomes that may have an effect on the subject's health or well-being; and
 - A procedure to determine when and how to notify individual subjects or their health care providers of findings that may affect the subjects' health.
 - **Differentiating Usual Care from Research.** This means the investigator provides for usual care. If the protocol involves "usual care," the protocol must either include a narrative section or there must be a separate document in the IRB application that clearly differentiates the research intervention(s) from "usual care" (whether the "usual care" is limited to one "arm" of the study or is being delivered to all study subjects).
 - When a study involves "usual care," in the protocol or a separate document in the IRB application the investigator must clearly designate the individual or entity (e.g., the appropriate research personnel versus the subject's health care provider) responsible for relevant aspects of both the research and the usual care.
 - The subject needs to be able to identify which activity (e.g., treatment or service) is research, and which is usual care, and know who (the researcher or the subject's health care provider) is responsible for:



- Explaining potential risks and benefits of the treatment or service to the subject;
 - Providing the treatment or service;
 - Monitoring the treatment or service, as applicable;
 - Defining whether the adverse events result from usual care or research, as applicable;
 - Alerting the subject if there is a problem with the treatment or service (e.g., a newly discovered risk, a product recall); and
 - Documenting the subject's clinical course while receiving the treatment or service, as applicable.
- The researcher and the subject's health care provider may be the same individual. If they are different individuals, and the subject's health care provider is not involved in the research study, the health care provider is not considered to be a member of the research team.
- Enlisting Clinical Expertise. This means the investigator provides for clinical expertise. If the investigator is not a clinician, when appropriate, the protocol must have provisions for enlisting the services of a clinician with appropriate expertise and privileges to perform duties that may include, but not be limited to:
 - Reviewing the data, adverse events, and new study findings; and
 - Making required decisions to protect the health of the subject (e.g., stopping the participant's involvement in the study or determining when to notify the subject or the subject's health care provider of information that may affect the health of the subject).
 - Providing for Privacy and Confidentiality. This means the investigator provides for privacy and confidentiality. To facilitate review of the protocol by the Privacy Officer, the investigator must either dedicate specific sections of the protocol to privacy and confidentiality, or the investigator must develop an additional document that specifically addresses all privacy and confidentiality issues in the protocol; this becomes part of the IRB protocol file. The description needs to be sufficiently specific for the reader to understand how this requirement protects the subject's privacy and the confidentiality of the data. These procedures must be in compliance with all applicable VA and other Federal requirements.
 - Providing for Information Security. This means the investigator provides for an information security plan. To facilitate review of the protocol by the Information Security Officer, the investigator must either dedicate specific sections of the protocol to information security, or the investigator must develop an additional document that specifically addresses all information security issues in the protocol; it becomes part of the IRB protocol file. The plan must clearly identify and include, but not be limited to:
 - Whether or not individually identifiable information is to be collected or used;
 - How the data is to be collected or acquired;
 - Where the data (original and all copies) is to be stored and corresponding security systems;
 - How the data is to be transported or transmitted from one location to another;



- Who is to have access to the data and how they are to access it (anyone who has access to the data is responsible for its security);
- All entities or individuals outside VHA to whom the data is to be disclosed, and the justification for such disclosure and the authority (e.g., the HIPAA authorization);
- Who is to have access and be responsible for the security of the information (e.g., the Coordinating Center, the statistician, and principle investigator who has ultimate responsibility);
- Mechanisms used to account for the information;
- Security measures that must be in place to protect individually identifiable information if collected or used; and
- How and to whom a suspected or confirmed loss of VA information is to be reported.
- Providing Special Safeguards. This means the investigator provides for special safeguards. When applicable, the protocol includes a narrative section that:
 - Identifies any circumstances that may warrant special safeguards to protect the rights and welfare of subjects who are likely to be vulnerable including, but not limited to, those subjects who may be susceptible to coercion or undue influence; and
 - Describes appropriate actions to provide such safeguards.
- Providing for Reuse of Data. This means the investigator, if the data may be reused in other studies, describes the research data repository in which the data is to be stored. There must be a research informed consent and a HIPAA authorization associated with the protocol unless these requirements are waived by the IRB. If the IRB does not waive the requirements then the informed consent and HIPAA authorization content must include language on the uses and disclosures of the data as defined in the protocol as well as information on how privacy and confidentiality will be maintained and how the data will be secured. If the creation and operation of the data repository is not included in the data collection protocol, there must be a separate IRB-approved protocol for the creation and operation of the data repository.
- When a subject experience adverse events while undergoing clinical care that is part of a research study, the clinical care adverse events must be disclosed to subjects in accordance with current VHA policy.
- Other specific requirements of Veterans Administration (VA) research be found in the “Additional Criterion for Veterans Administration (VA) Research” section in the IRB’s “WORKSHEET: Criteria for Approval and Additional Considerations (HRP-311).”
- Keep the original signed copy of the signed and dated consent document in the subject’s research records. Place a copy of all signed and dated consents documents placed into the subject's 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 facilities as in-patients, treated as outpatients at VA facilities, or when research



procedures or interventions are used in the medical care of the VA research subject at a VA facility or at facilities contracted by VA to provide services to Veterans (e.g., contract CBOCs or contract nursing homes).

- A record must be created:
 - When the research requires use of any clinical resources, such as: radiology, cardiology (e.g., electrocardiogram, stress test, etc.), clinical laboratory, and pharmacy; or
 - If the research intervention may lead to physical or psychological AEs.
- At a minimum, the health record must include the following information for an approved research study:
 - The name of the study;
 - The person obtaining the subject's informed consent;
 - A statement that the subject or the subject's legally authorized representative was capable of understanding the informed consent process;
 - A statement that the study was explained to the subject or the subject's legally authorized representative;
 - A statement that the subject or the subject's legally authorized representative consented before participation in the study began;
 - A statement that the subject or the subject's legally authorized representative was given the opportunity to ask questions;
 - A copy of the signed and dated research informed consent form;
 - A copy of the HIPAA authorization for data use or disclosure;
 - A copy of the initial enrollment progress note and other applicable progress notes;
 - Information on possible drug interactions and/or toxicity of the pharmaceutical agents that are being administered to the subject because of the research (i.e., investigational drugs);
 - VA Form 10-9012, Investigational Drug Information Record, or superseding forms for investigational drugs;
 - A copy of any research results that are used for medical careInformation on all research and experimental interventions including potential risks, indications, and applicable progress notes; and
 - VHA Form 10-3203, Consent for Use of Picture and/or Voice, if applicable.
- A method to identify clinic visits solely for research (such as a note title) must be used to differentiate those visits from any other clinic visits. The research titled note may be included in the Crisis, Warnings, Allergies and/or Adverse Reactions, and Directives (CWAD) alerts.
- Clinic visits and inpatient care for research purposes must be coded as non-billing events.



- When access to patient health records is no longer required for a study, the study has been completed, or when authorization is revoked, the investigator or designee, must notify the facility HIM program manager and, if applicable, the Information Security Officer.
- **Flagging of the medical record:**
 - The patient health record must be flagged if the subject's participation in the study involves:
 - Any invasive research procedure (e.g., muscle biopsy or bronchoscopy);
 - Interventions that will be used in the medical care of the subject, or that could interfere with other care the subject is receiving or may receive (e.g., administration of a medication, treatment, or use of an investigational device);
 - Clinical services that will be used in the medical care of the subject (e.g., orders for laboratory tests or x-rays ordered as a part of the study), or that could interfere with other care the subject is receiving or may receive; or
 - The use of a survey or questionnaire that may provoke undue stress or anxiety unless the IRB determines that mandatory flagging is not in the best interests of the subject (e.g., an interview study of victims of sexual assault).
 - The patient health record must be flagged if the IRB determines if flagging is necessary.
 - If IRB determines and documents that the patient health record must be electronically flagged in Computerized Patient Record System (CPRS) as participating in a research study then, the health record must:
 - Identify the investigator, as well as contact information for a member of the research team that would be available at all times. NOTE: The research team must have an appropriate member available (on-call) at all times.
 - Contain information on the research study or identify where this information is available.
 - The duration of flagging is determined by local policy.
- **Vulnerable Subjects**
 - Whenever VA has more stringent requirements than DHHS for protection of vulnerable individuals or vulnerable populations as research subjects, all VA requirements must be met.
 - Where relevant, the IRB needs to document why it considers an individual or population to be vulnerable, and that adequate safeguards have been included in the study to protect the rights and welfare of subjects who are likely to be vulnerable.
 - Individuals or populations that may be temporarily or permanently vulnerable include, but are not limited to, those who:



- Are susceptible to coercion or undue influence (e.g., the homeless, prisoners, students, patients with limited or no treatment options, socially and economically disadvantaged).
- Lack comprehension of the research and its potential risks (e.g., educationally disadvantaged, dementia, schizophrenia, depression).
- Have increased susceptibility to harm from the procedures of the specific study under review (e.g., individuals who would have to answer study survey questions about their sexual assault).
- Are at risk for economic, social, or legal consequences from the study (e.g., individuals who would have to answer study survey questions about their drug use or HIV status).
- 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. Research related to neonates including, but not limited to, observational or interventional research, must not be conducted by VA investigators while on official duty, or at VA facilities, or at VA approved off-site facilities.
 - Pregnant Women
 - Prisoners
 - Children
 - Subjects who Lack Decision-making Capacity.
- Women of child bearing potential may not be entered into studies involving the use of FDA Categories for Drug Use in Pregnancy's Category D or X drugs unless a waiver is obtained from the Chief Research and Development Officer.
- If a subject becomes incarcerated during the course of a study:
 - Investigators must notify the IRB as soon as they become aware that the subject has been incarcerated.
 - The investigator must make a determination as to whether or not it is the best interests of the subject to remain in the study, or if the subject can be safely withdrawn from the study.
 - If the investigator determines it is in the best interest of the subject to remain in the study, the subject's continued participation in the study is contingent on the IRB's reviewing and approving such participation. The IRB approval must comply with 45 CFR 46.301-306.
 - After IRB and other relevant approvals (e.g., from the penal system) for the incarcerated subject's continued participation in the study have been obtained, a waiver must also be obtained from the Chief Research and Development Officer.



- The investigator must comply with all applicable requirements including, but not limited to, applicable court, penal system, and local, VA, and other Federal requirements.
- **Research Involving Children**
 - Research involving children cannot be conducted by VA investigators while on official VA duty, using VA resources, completely or partially in a VA facility or at a VA-approved off-site facility unless a waiver has been granted by the Chief Research and Development Officer. For purposes of this Handbook, research involving biological specimens or data obtained from children is considered to be research involving children.
 - Prior to requesting a waiver, the following criteria must be met:
 - The study represents no greater than minimal risk as determined by the IRB.
 - The study meets all requirements in 45 CFR 46, Subpart D, Additional Protections for Children Involved as Subjects in Research, Sections 46.401 through 46.404, and 46.408.
 - The IRB reviewing the study has appropriate membership to represent children's interests and pediatric expertise.
 - The IRB reviewing the study has specific SOPs regarding children in research.
 - The VA facility Director certifies that the facility is able to respond to pediatric emergencies if the study includes interactions with children at the VA facility.
 - If the sponsor of the research is not VA, the facility Director makes certain that the sponsor of the research has procured appropriate liability insurance.
 - To request a waiver, the following information must be submitted to ORD for each protocol:
 - A cover letter signed by the VA facility Director that contains the following information:
 - Certification by the VA facility Director that the facility is able to respond to pediatric emergencies if the study includes an interaction with children at the VA facility.
 - Any additional safeguards that have been incorporated into the clinical site where children will be studied.
 - Information on the study's funding source and on liability coverage if the sponsor is not VA.
 - Certification that the IRB has determined the study to be of no greater than minimal risk and has approved the study.
 - A statement that the required elements of 45 CFR 46 Subpart D have been met.
 - A description of the relevance to Veterans' health of both the study and the inclusion of children in the study.



- A copy of the study protocol, the informed consent form, the assent document, and HIPAA authorization. The informed consent document signed by the parent or guardian is the vehicle for parent or guardian permission. Provisions for permission by parents or guardians must be documented in accordance with and to the extent required by 38 CFR 16.117.
- Minutes of the IRB meeting approving the study. The IRB minutes need to reflect the discussion regarding level of risk, the informed consent and assent forms, the investigators' qualifications to conduct research involving children, and any additional safeguards incorporated into the protocol.
- If the study involves biological specimens or data collected from children, in addition to the preceding requirements, the following must be submitted:
 - A discussion of how the biological specimens or data were, or will be, obtained and under what consents or authorization.
 - If the biological specimens or data were, or will be, collected for research purposes, the IRB approval, the informed consent form, and the HIPAA authorization for the research.
 - If biological specimens or data were, or will be, collected from an international site, a waiver from the Chief Research and Development Officer for international research.
 - Plans for future use of biological specimens or data.
- Research Involving Persons Who Lack Decision-Making Capacity
 - Persons who lack decision-making capacity are not to be subjects in research simply because they are readily available.
 - No individual who lacks decision-making capacity may participate in VA Research until the IRB has reviewed and approved that individual's, or that class of individuals', participation in a given study.
 - An individual is presumed to have decision-making capacity unless any one or more of the following apply:
 - It has been documented by a qualified practitioner in the individual's medical record in a signed and dated progress note that the individual lacks capacity to make the decision to participate in the proposed study. NOTE: The qualified practitioner may be a member of the research team.
 - The individual has been ruled incompetent by a court of law.
 - The investigator has consulted with a qualified practitioner (who may be a member of the research team) about the individual's decision-making capacity before proceeding with the informed consent process.



- Individuals, who because of a known condition, are at high risk for temporary (e.g., head trauma) or fluctuating (e.g., schizophrenia) lack of decision-making capacity must be evaluated by a qualified practitioner (who may be a member of the research team), to determine the individual's ability to provide informed consent. This evaluation must be performed as described in the IRB-approved protocol. If the individual is deemed to lack decision-making capacity at the time of their participation in the study, a legally authorized representative must provide informed consent. If the subject regains decision-making capacity, the investigator or designee must repeat the informed consent process with the subject, and obtain the subject's permission to continue with the study.
- When you are a local investigator for a multi-site study, you must:
 - Conduct the study according to the most recently approved version of the protocol, the most recently approved version of the informed consent form, the most recently approved version of the HIPAA authorization, and all applicable local, VA and other Federal requirements;
 - Ensure that all amendments and modifications to the protocol and the informed consent form are submitted to and approved by the local IRB of record prior to initiating any changes;
 - Report any unanticipated internal or local SAEs, whether related or unrelated to the research;
 - Report study events and interim results (if available) to the local IRB of record as required by local IRB policies; and
 - Oversee all aspects of the study at your site.
- Research Involving Human Biological Specimens: All activities involving the collection of human biological specimens for research purposes, as well as the research use of specimens collected for clinical care, must be conducted under the terms of an approved research protocol. The collection and use of human biological specimens (either identifiable or de-identified) must comply with all applicable VA and other Federal requirements including, but not limited to: 21 CFR 50, 21 CFR 312, 38 CFR 16, 45 CFR 46 D (if research involves specimens from children), 45 CFR 160 and 164 (HIPAA), VHA Handbook 1200.8, and current VA requirements for research involving human biological specimens or superseding requirements.
- Research Involving Human Data:
 - Use of VA or non-VA human data and data repositories (whether developed for health care, administration of VA programs, or research) for research purposes must be consistent with the mission of VA including:
 - Having relevance to the health of Veterans,
 - Protecting the privacy of the individuals from whom the data were collected, and
 - Being consistent with all applicable ethical and regulatory standards, and all applicable VA and other Federal requirements.
 - Information from DNA sequencing is considered human subjects data.



- **Research Involving Collection Of Data From Voice, Video, Or Photographs Made For Research Purposes**
 - Informed consent for research must be obtained from each research subject before taking photographs or making voice or video recordings that will be used for research purposes.
 - Unless IRB grants a waiver of documentation of informed consent for research, the informed consent form for research must include a discussion of why photographs, or voice or video recordings are being taken for the research, who will have access to them, and what their disposition will be after the research is completed.
 - VA Form 10-3203 documents permission for pictures, video, and voice recordings to be made or taken.
 - In the conduct of research, VA Form 10-3203 must be used in accordance with applicable VA and VHA policy.
 - When the research subject is a patient (either an inpatient or outpatient):
 - The subject must sign VA Form 10-3203 to permit photographs or video and voice recordings that will be used for research purposes even if the IRB has waived the requirement for documentation of informed consent for research.
 - Photography or recordings cannot occur prior to the patient's granting such permission.
 - The subject's signed and dated VA Form 10-3203 must be placed into the medical record along with, if applicable, the signed and dated research informed consent form, even if the IRB has waived documentation of informed consent for research.
 - VA Form 10-5345 documents permission for the disclosure of medical records or health information, including pictures, video, and voice recordings to another individual.
 - In the conduct of research, VA Form 10-5345 must be used in accordance with applicable VA and VHA policy.
- **International Research:**
 - Research conducted at U.S. military bases, ships, or embassies is not considered international research.
 - All individuals who participate as subjects in research at international sites must be provided appropriate protections that are in accord with those given to research subjects within the U.S., as well as protections considered appropriate by local authority and custom at the international site (38 CFR 16.101(g)).
 - VA international research is defined as any VA-approved research conducted at international sites (not within the U.S., its territories, or Commonwealths); any VA-approved research using either human biological specimens (identified, de-identified, or coded) or human data (identified, de-identified, or coded) originating from international sites; or



any VA-approved research that entails sending such specimens or data out of the U.S.

- This includes sending such 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). It also includes a VA's serving as a coordinating center for an international research project.
- Multi-site trials are covered under this definition if any of the following apply:
 - VA is a sponsor;
 - VA functions as the coordinating center;
 - VA subcontracts to a foreign site;
 - The investigator for the total study is a VA investigator; or
 - The VA investigator is specifically collaborating with an international investigator and the VA investigator sends data or human biological specimens outside the U.S., or receives them from outside the U.S.
 - NOTE: This requirement does not apply if VA is only one of the participating sites and the trial does not meet the preceding conditions.
- Permission must be obtained from the CRADO, or designee, prior to initiating any VA-approved international research.
 - This applies regardless of the funding source (funded or unfunded) and to research conducted through any mechanism of support including agreements, MOU, Cooperative Research and Development Agreements (CRADA), grants, or contracts.
 - The CRADO, or designee, will not grant permission for an international research study involving prisoners as research subjects.
- All international sites must hold an international FWA, and the research must be approved by the IRB or Research Ethics Board of the participating site(s) that are listed on the international FWA.
- When conducting international research, the investigator is responsible for:
 - Obtaining approval from the facility Director.
 - Obtaining permission from the CRADO, or designee, in writing before initiating an international research study.
 - Conducting research in compliance with this Handbook, and all other applicable VA and other Federal requirements including those for protecting human subjects, tissue banking, use of databases, Federal criminal laws, and the Standards of Ethical Conduct for Employees of the Executive Branch.
- Use Preparatory To Research: Data repositories (including VA medical records) may be used (i.e., accessed) by VA investigators for activities that are preparatory to VA research without the requirement to obtain either a HIPAA authorization



from the subject or waiver of HIPAA authorization by an IRB or Privacy Board. This includes use of PHI for the preparation of a research protocol prior to submission to the IRB(s).

- “Preparatory to research” activity is the only instance of access for research purposes allowed in VHA without a written HIPAA authorization signed by the individual, a waiver of HIPAA authorization by an IRB or Privacy Board, or approval by the IRB(s). This access is granted only to VHA researchers.
- Non-VHA researchers may not access VHA data for reviews preparatory to research. Additionally, the following holds true:
- The investigator must make the representations necessary for preparatory access as required by the HIPAA Privacy Rule and document it in the investigator's research files. The representations required by the HIPAA Privacy Rule are:
 - (1) The access to PHI is only to prepare a protocol;
 - (2) No PHI will be removed from the covered entity (i.e., VHA); and
 - (3) The PHI accessed is necessary for preparation of the research proposed.
- Only aggregate data may be recorded in the researcher’s files, and these aggregate data may be used only 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 targets or sample size requirements.
- Individually identifiable health information may not be recorded.
- Data or information reviewed may not be used for contacting or recruiting subjects.
- Investigators must comply with all other access requirements set by the repository of interest.
- Requirements for Data Use Agreements (DUA) or Data Transfer Agreements (DTA) must be met.
- Pilot studies are full-fledged research studies that must be approved by the IRB(s), when human subjects are involved. Pilot studies are not considered to be “activities preparatory to research.”
- No formal IRB determination of exemption from human subject protection requirements is needed if all of the conditions listed in paragraph 57 are satisfied.
- Participation Of Non-Veterans As Research Subjects: VA research needs to be relevant to Veterans or active duty military personnel. The investigator must justify including non-Veterans in a VA research protocol, and the IRB must review the justification for inclusion of non-Veterans and specifically approve entering non-Veterans into the study before any non-Veterans can be recruited. The IRB must appropriately document in the IRB minutes or IRB protocol file its determinations regarding participation of non-Veterans in the study.



- 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).
- Other Research. Non-Veterans may be entered into an approved VA research study when the investigator can present a compelling argument to the IRB for the inclusion of non-Veterans (e.g., insufficient number of Veterans; survey of VA employees; study of active duty military; study involving Veterans' family members), and the research is relevant to the care of Veterans or active duty military personnel.
- VA regulations require the VA to provide care for all research-related injuries including those studies that are considered minimal risk.
- VA regulations pertaining to research involving human participants do not permit data obtained from patients to be classified as human participant research (as those terms are defined by VA regulations), nor may the outcome of such care be included in any report of a research activity subject to VA regulations pertaining to research involving human participants (as those terms are defined by VA regulations).