

HUMAN RESEARCH PROTECTION PROGRAM: INVESTIGATOR MANUAL

HRP 103
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Human Research Protection Program
UNIVERSITY OF GEORGIA

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What is the purpose of this manual?

This document “INVESTIGATOR MANUAL (HRP-103)” is designed to guide the Principal Investigator and study team members through current policies and procedures related to the conduct of Human Research by the University of Georgia (UGA). Throughout this document, “institution” refers to the UGA.

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?”

What is Human Research?

The “HUMAN RESEARCH PROTECTION PROGRAM PLAN (HRP-101)” and [Policy and Procedures: Determination of Human Subjects Research](#) define the activities that this institution considers to be “Human Research.” You can only conduct Human Research with prior Institutional Review Board (IRB) review and approval (or an IRB determination that the Human Research is Exempt). Activities that do not meet the definition of Human Research do not require review and approval by the IRB and do not need to be submitted to in the IRB Portal unless a formal determination is needed.

An algorithm for determining whether an activity is Human Research can be found in the “WORKSHEET: Human Research Determination (HRP-310),” located in the IRB Portal Library. Use this document for guidance to determine if an activity meets either the DHHS or FDA definition of Human Research in questionable cases. The IRB makes the ultimate determination as to whether an activity constitutes Human Research subject to IRB oversight.

If you have questions about whether an activity is Human Research, contact the Human Subjects Office (HSO).

What is the Human Research Protection Program?

The document “HUMAN RESEARCH PROTECTION PROGRAM PLAN (HRP-101)” describes this institution’s overall plan to protect subjects in Human Research.

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

How do I submit new Human Research to the IRB?

All applications must be submitted via our electronic system. Login to the IRB portal which is designed to gather information and materials necessary to evaluate and approve research in accordance with human subjects regulations ([45 CFR 46](#)) and applicable policies . Attach/upload all requested materials and maintain electronic copies of all information submitted in case revisions are required.

What training do I and my study team members need to conduct Human Research?

Investigators and personnel engaged in conducting human subjects research must complete the online Collaborative Institutional Training Initiative (CITI) human subjects training program. Either the Social and Behavioral or the Bio-Medical Basic Course must be completed. Training is valid for five-years, after which time a refresher CITI course must be completed. However, NIH-funded investigators and research staff who are involved in clinical trials are required to maintain their Good Clinical Practice (GCP) training every three years through the CITI refresher course. All training can be accessed at PEP.uga.edu.

Please note that submissions in the IRB portal will only be accepted if the Principal Investigator and members of the research team have satisfied this training requirement and that training is current (or will not expire in 30 days). If training will expire within 90 days of submission, the submission will be accepted and reviewed by the IRB but final approval will be granted only after all personnel engaged in Human Research have successfully completed the refresher course.

When specific populations (e.g., prisoners, children) are included and/or the research involves specific procedures (e.g., review/use of protected health information, online data collection), additional modules may be required.

What financial conflicts of interest must I and my study team members disclose to the IRB?

The Principal Investigator and study team members must disclose all conflicts of interest for themselves and their immediate family members for any Human Research in accordance with the [UGA Policy on Conflicts of Interest in Sponsored Projects](#). The IRB has the final authority to determine whether conflicts of interest and its management allow the research to be approved. For additional information, see [Policy and Procedure: Financial Conflicts of Interests](#).

How do I create a consent document?

Use one of the Consent Templates in the IRB Portal Library or the HRPP website as a guide to create a consent document that is appropriate for your study.

Note that consent documents for non-exempt Human Research must contain all of the required and applicable additional/optional elements of informed consent disclosure. Review the “Informed Consent Elements Checklist” in the portal Library to ensure that these elements are addressed. To help you track the most recent version of the Consent Form submitted to (and

approved by the IRB), we recommend that you use file names that include version identifications in the portal submission and in your separate electronic files.. Consent documents for non-exempt Human Research with a signature block will be stamped with an approval period following IRB review and approval.

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

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

- **Not “Human Research”**: Activities must meet the DHHS or FDA definition of “research” involving “human subjects” for the activity to fall under IRB oversight. Activities that meet neither definition of “Research involving “Human Subjects” are not subject to IRB oversight or review. Review the WORKSHEET – 310 - Human Research Determination” in the IRB Portal Library for reference. Contact the Human Subjects Office in cases where it is unclear whether an activity meets the regulatory definition of Human Research.
- **Developmental Review** (§46.118 Determination): Certain grant applications and proposals lacking definite plans for involvement of human subjects may qualify for Developmental Review. This determination is only granted by the Human Subjects Office to satisfy the funding agency’s requirements or to allow investigators to have access to funding to begin aspects of the project that do not involve human subjects. These applications need not be reviewed by an IRB before an award may be made. However, no human subjects may be involved in any project supported by these awards until the IRB has reviewed and approved the human research activities in the project.
- **Exempt**: Certain categories of Human Research may be exempt from regulations but require determination that they are exempt from someone other than the researcher. It is the responsibility of the Human Research Protection Program (HRPP) Staff to determine whether Human Research is exempt. Review the CHECKLIST – 312 - Exempt Determination” for reference on the categories of research that may be exempt.
- **Review Using the Expedited Procedure**: Certain categories of non-exempt Human Research may qualify for review using the expedited procedure. These studies are reviewed by a designated IRB reviewer(s) and not by a convened IRB. Review the “WORKSHEET – 313 - Eligibility for Review Using the Expedited Procedure” 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 or Approved – Modifications Required: Made when IRB members require specific modifications to the research before approval can be finalized.
- Tabled: Made when the IRB cannot approve the research at a meeting for reasons unrelated to the research, such as loss of quorum. When taking this action, the IRB automatically schedules the research for review at the next available convened meeting.
- Deferred: Made when the IRB determines that the Board is unable to approve research and the IRB suggests modifications that might make the research approvable. When making this motion, the IRB describes its reasons for this decision, describes modifications that might make the research approvable, and gives the investigator an opportunity to respond to the IRB in person or in writing.
- Disapproval: Made when the IRB determines that it is unable to approve research and the IRB cannot describe modifications that might make the research approvable. When making this motion, the IRB describes its reasons for this decision and gives the investigator an opportunity to respond to the IRB in person or in writing.

How does the IRB decide whether to approve Human Research?

The criteria for exempt determination or can be found in the “CHECKLIST – 312 - Exempt Determination” , the “WORKSHEET - 314- Criteria for Approval and Additional Considerations” for research eligible for Expedited review, and WORKSHEET – 325 – Meeting Approval Criteria and Determinations for research reviewed at convened meetings. These worksheets may reference other materials that might be relevant. All checklists and worksheets can be found on the IRB Portal Library.

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

What will happen after IRB review?

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

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

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

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

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

What are my obligations and responsibilities after IRB approval?

- 1) Start Human Research activities only after you have received the final IRB approval/determination letter.
- 2) Start Human Research activities only after you have secured all other required approvals or authorizations from departments/units or institutions prior to commencing research that involves their resources.
- 3) Report immediately to the IRB if an approved study or study under review has received any external funding or support (federal or non-federal).
- 4) Ensure that there are adequate resources to carry out the research safely. This includes, but is not limited to, sufficient investigator time, appropriately qualified research team members, equipment, and space.
- 5) Ensure that 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.
- 6) Ensure that every research personnel's required CITI training is kept current during the duration of the study, and that a study team member whose CITI training has expired is not allowed to participate in Human Research activities.
- 7) Monitor the financial conflicts of interest of research personnel (and their immediate family members), and disclose to the IRB within 30 days any new financial interest acquired or discovered, or during the submission of continuing review or modification to an approved study.
- 8) Monitor the approval period and approval expiration dates or progress report due dates and for submitting required progress reports or closures in accordance with institutional policy requirements.
- 9) Personally conduct or oversee the Human Research in accordance with all applicable federal, state, and local laws and regulations, international laws, institutional policies, and requirements or determinations of the IRB.
 - a) Conduct the Human Research in accordance with the relevant current protocol as approved by the IRB.
 - b) When required by the IRB, ensure that consent or permission is obtained and documented (if applicable) in accordance with the relevant current IRB-approved protocol and using the current IRB-approval materials.
 - c) Do not modify non-exempt Human Research without prior IRB review and approval except if changes in protocol are necessary to eliminate apparent immediate hazards to the human participants. Do not modify exempt Human Research without prior IRB

review and approval except if modifications are minor and will not disqualify the research from an exempt determination; see *Policy and Procedures: Exempt Research*.

- d) Protect the rights, safety, and welfare of subjects involved in the research and ensure that the participants' rights and welfare take precedence over the goals and requirements of the study.
- e) When research is covered by a [Certificate of Confidentiality](#), ensure that:
 - i) the Certificate of Confidentiality will not be used to coerce individuals to participate in the research project;
 - ii) all subjects will be informed that a Certificate has been issued, and they will be given a description of the protection provided by the Certificate and disclosures outside the scope of coverage of the Certificate per 42 U.S.C. 241 (d)(1)(C) (e.g., as required by Federal, State, or local laws for public health reporting or for child or elder abuse reporting, if necessary for the medical treatment of the participant, or when it is made with the consent of the participant or for the purpose of other scientific research that is in compliance with Federal regulation (e.g., 45 CFR 46);
 - iii) any research participant entering the project after expiration or termination of the Certificate will be informed that the protection afforded by the Certificate does not apply to them;
 - iv) the name of the individual or any information, documents, or biospecimens that contain identifiable sensitive information about the individual, and that was created or compiled for the research, is not disclosed or provided to any other person not connected with the research (42 U.S.C. 241(d)(1)(B));
 - v) the name of the individual or any information, documents, or biospecimens that contain identifiable sensitive information about the individual and that was created or compiled for the research is not disclosed or provided in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding (42 U.S.C. 241 (d)(1)(D));
 - vi) informing any other institution or researchers receiving identifiable sensitive information about the Certificate protections as they apply to the data/specimens in perpetuity and secondary research conducted with Certificate-protected information is subject to the same rules as the initial research (Bankert, et.al, Institutional Review Board Management and Function, 3rd edition, 2021, Jones and Bartlett, pp. 422-423.)

10) Submit to the IRB:

- a) Proposed modifications before they are implemented as described in this manual. (See "How do I submit a modification?") The only exception to this policy is in situations where changes in protocol are required to eliminate apparent immediate hazards to the human participants.
- b) A continuing review application as required in the approval letter for more than minimal risk research or for minimal risk research which the IRB has determined continuing review is necessary, no later than 30 days before the study expires, if data collection and/or analysis of individually-identifiable information will continue after the expiration date. (See "How do I submit continuing review?")

- c) A progress report application as requested in the approval letter for minimal risk research, no later than 30 days before the progress report due date. (See “How do I submit a progress report?)
 - d) A request to close the study upon completion of all Human Research activities or in the event that the study was never initiated. (See “How Do I Close Out a Study?”)
- 11) Promptly report to the IRB any unanticipated problems or incidents involving risks to subjects or others and other information items in accordance with the time frame and reporting requirements described in Appendix A. In the IRB Portal, create a reportable new information submission, and submit with all required supporting documents. Investigators should not delay reporting for lack of complete information; follow-up information may be submitted as more information becomes available. The IRB will review all reports and make decisions regarding the need to suspend the research and/or modify procedures and consent documents. If there are any questions about whether an event is reportable, contact the Human Subjects Office.
- 12) Maintain all pertinent research records (regardless of media type) that are created by and/or in the possession of the researchers for at least three (3) years after completion of the study (e.g., raw data; signed consent form(s) for each research participant, if applicable). Records that involved protected health information is subject to Health Insurance Portability and Accountability Act (or HIPAA) requirements and must be retained for a minimum of six (6) years after each subject signed an authorization.
- 13) During the conduct of Clinical Trials:
- a) Ensure appropriate use of the investigational product, as described in the protocol, in the current investigator brochure, in the product information, and in other information sources provided by the sponsor.
 - b) Ensure that a qualified physician or medical professional (either the PI or sub-investigator for a clinical trial) is responsible for all clinical trial-related medical decisions.
 - c) Ensure that adequate medical care is provided to a participant for any adverse events related to the clinical trial (including clinically significant laboratory values) during and following a participant’s participation in a clinical trial.
 - d) Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.
 - e) Permit monitoring and auditing by the sponsor and inspection by the appropriate regulatory authority.
 - f) Maintain a list of appropriately qualified persons to whom you have delegated significant clinical trial-related duties.
 - g) Follow reporting requirements of sponsor, federal agencies, and IRB for unexpected serious adverse drug reactions.
 - h) Provide written reports to the sponsor, the IRB, and, where applicable, the university on any changes significantly affecting the conduct of the clinical trial or increasing the risk to participants.
 - i) Maintain the clinical trial documents as required by the sponsor, federal agencies, and the IRB. Ensure that essential documents are retained until at least two 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 two years have elapsed since the formal discontinuation of clinical development of the investigational product.

- j) If the PI terminates or suspends a clinical trial without prior agreement of the sponsor, inform the university, sponsor, and the IRB.
- k) If the IRB terminates or suspends approval of the clinical trial, promptly notify the sponsor.
- l) Upon completion of the clinical trial, submit to the IRB a summary of the trial's outcome, and submit any required reports to appropriate regulatory agencies.

14) See additional requirements of various federal agencies in Appendices B-1 to B-8.

How do I document consent?

The IRB considers a signed consent/parental permission form as documentation of informed consent. Use the most recently approved version of the consent document (check that dates are valid) to make copies for use when obtaining consent. The following are the requirements for signed 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 or the sponsor, the subject's or representative's signature is to be witnessed by an individual who signs and dates the consent document.
- For subjects or representatives 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.

How do I submit a modification?

Create a modification request in the IRB portal and attach all requested materials. Maintain electronic copies of all information submitted to the IRB in case revisions are required. Please note that research must continue to be conducted without inclusion of the modification until IRB approval is received.

- For portal IDs that begin "STUDY", search for and open the initial submission record. Select Create Modification on the study workspace in the portal. Select Modification as the purpose of the new submission where prompted
- For portal IDs that begin "PROJECT", search for and open the initial submission record. Select Create Version on the study workspace in the portal. Select Modification as the purpose of the version where prompted.

How do I submit continuing review?

For more than minimal risk Human Research or minimal risk Human Research which the IRB has determined requires continuing review, complete and submit a request for Continuing Review in the IRB portal and attach all requested materials, no later than 30 days before the

study expires. Maintain electronic copies of all information submitted to the IRB in case revisions are required.

If the continuing review involves modifications to previously approved research, these can be combined with the request for continuing review.

If the approval of Human Research expires, all Human Research procedures related to the project must cease, including recruitment, advertisement, screening, enrollment, consent, interventions, interactions, and collection or analysis/use of private identifiable information. Continuing Human Research procedures without current approval is a violation of UGA policy. If subjects already enrolled will be harmed by stopping Human Research procedures that are available outside the Human Research context, provide these on a clinical basis as needed to protect current subjects. If current subjects will be harmed by stopping Human Research procedures that are not available outside the Human Research context, immediately contact the Human Subjects Office and provide a written list of the currently enrolled subjects and why they will be harmed by stopping Human Research procedures.

How do I submit a Progress Report

For minimal risk Human Research which the IRB has determined does not require continuing review, complete and submit a Progress Report in the IRB portal no later than 30 days before the due date for the Progress Report. Maintain electronic copies of all information submitted to the IRB in case revisions are required.

How do I close out a study?

Submit a Close Study request in the IRB portal. Respond to all required questions and attach any required materials.

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.

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

Contact the Human Subjects Office or IRB Chair immediately to discuss the situation. If there is no time to make this contact, see the “322- UGA WORKSHEET: Emergency Use” for the regulatory criteria allowing such a use and make sure these are followed. Use the “TEMPLATE EMERGENCY USE CONSENT DOCUMENT (HRP-506)” to prepare your consent document. You will need to submit a report of the use to the IRB within five days of the use and for drugs and biologics, submit an IRB application for initial review within 30 days.

If you fail to submit the report within five 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.

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

Individuals getting an unapproved drug, biologic, or device without prior IRB review 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 get additional information and answers to questions?

This document and the policies and procedures for the Human Research Protection Program are available on the IRB Web Site at <http://research.uga.edu/hso/irb-guidelines/>.

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

212 Tucker Hall
University of Georgia
310 East Campus Road
Athens, GA 30602
Email: IRB@uga.edu
(706) 542-3199

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

Appendix A Reporting Events and Information to the IRB

A. Reportable Events and Information

1. Any serious adverse harm or injury (physical, psychological, social or economic) or other unanticipated events related or possibly related to participation in a research study. A Serious Adverse Event is any event associated with the subject's participation in research that:
 - 1.1. results in death;
 - 1.2. is life threatening (places the subject at immediate risk of death from the event as it occurred);
 - 1.3. requires in-patient hospitalization or prolongation of existing hospitalization;
 - 1.4. results in a persistent, significant or permanent disability/incapacity;
 - 1.5. results in a congenital anomaly/birth defect;
 - 1.6. any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed above (examples of such events include allergic bronchospasm (a serious problem with breathing) requiring intensive treatment in the emergency room or at home, blood dyscrasias (disorders) or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Reporting Timeframe: Unless a different reporting requirement is required by a federal agency or sponsor, an unanticipated problem or event which resulted in a subject's death, was life threatening, or places subjects or others at greater risk of harm than was previously known or recognized must be reported to the IRB within 24 hours of the principal investigator or any member of the investigative team becoming aware of the event. All other events must be reported to the IRB within 72 hours of the principal investigator or any member of the investigative team becoming aware of the event.

2. Information that indicates a new or increased risk, or a new safety issue, such as:
 - 2.1. New information (e.g., an interim analysis, data safety monitoring report, publication in the literature, sponsor report, or investigator finding) indicating an increase in the frequency or magnitude of a previously known risk, or identifying a new risk
 - 2.2. Major protocol deviations, violations, or other accidental or unintentional changes to the protocol or procedures involving risks or with the potential to recur. The characterization of a violation or deviation as major in any particular case will depend on the specific facts and circumstances of that case. Examples of major violations or deviations may include, but are not limited to:
 - 2.2.1. Failure to obtain informed consent, i.e., there is no documentation of informed consent, or informed consent is obtained after initiation of study procedures;
 - 2.2.2. Enrollment of a subject who did not meet all inclusion/exclusion criteria;

- 2.2.3. Performing study procedure not approved by the IRB;
- 2.2.4. Failure to report serious unanticipated problems/adverse events involving risks to subjects to the IRB and (if applicable), to the sponsor;
- 2.2.5. Failure to perform a required lab test that, in the opinion of the PI, may affect subject safety or data integrity;
- 2.2.6. Drug/study medication dispensing or dosing error;
- 2.2.7. Study visit conducted outside of required time frame that, in the opinion of the PI or IRB, may affect subject safety;
- 2.2.8. Failure to follow safety monitoring plan.
- 2.3. Complaint or other unanticipated information which is related to the research that indicates subjects or others might be at increased risk of harm or at risk of a new harm
- 2.4. Revision in an investigator brochure, package insert, or device labeling that indicates an increase in the frequency or magnitude of a previously known risk, or identifies a new risk
- 2.5. Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a protocol
- 2.6. Change(s) significantly affecting the conduct of the study or increasing the risk to participants
- 2.7. Change(s) made to the protocol conducted without prior IRB approval to eliminate an apparent immediate hazard to a subject
- 2.8. Events requiring prompt reporting according to the protocol, sponsor, or funding agency
- 2.9. Suspension or termination by the sponsor, investigator, or institution
- 2.10. Breaches in confidentiality resulting from a disclosure of confidential information or from lost or stolen confidential information

Reporting Timeframe: The information described above should be reported to the IRB within 5 business days of the investigator's or research staff member's learning of the event.

- 3. Non-compliance with the federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance. See *Office of Research Compliance Policy and Procedure for Responding to Allegations of Research Noncompliance*.

Reporting Timeframe: The information described above should be reported to the IRB within 5 business days of the investigator's or research staff member's learning of the event.

B. External IRB

For external adverse events and research overseen by an external IRB, investigators should follow the reporting requirements of that IRB. However, a report to the UGA IRB should be submitted at least 5 business days after the submission of the report to the external IRB.

C. Submission

Reportable events are submitted using the IRB using Click IRB's reportable new information submission, and submit with all required supporting documents.

If the report cannot be completed in its entirety within the required time period, a preliminary report should be submitted. The report should be amended once the event is resolved and/or more information becomes available.

D. References

1. 45 CFR 46 Code of Federal Regulations for the Protection of Human Subjects
2. OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events s (January 15, 2007)
3. FDA Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs — Improving Human Subject Protection

Appendix B-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 subjects, investigators should explain whether already collected data about the subjects will be retained and analyzed even if the subjects choose to withdraw from the research.

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

Appendix B-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 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.

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

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

- 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 subjects under the investigator's care; and for the control of drugs under investigation.
 - ii. An investigator must, in accordance with the provisions of 21 CFR §50, obtain the informed consent of each human subject to whom the drug is administered, except as provided in 21 CFR §50.23 or §50.24 of this chapter.
 - iii. Additional specific responsibilities of clinical investigators are set forth in this part and in 21 CFR §50 and 21 CFR §56.
- c. Follow FDA requirements for control of the investigational drug⁵
 - i. An investigator must administer the drug only to subjects under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator.
 - ii. The investigator must not supply the investigational drug to any person not authorized under this part to receive it.
- d. Follow FDA requirements for investigator recordkeeping and record 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 subjects.
 - 2. If the investigation is terminated, suspended, discontinued, or completed, the investigator must return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 21 CFR §312.59.
 - ii. Case histories.
 - 1. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation.
 - 2. Case histories include the case report forms (CRFs) and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital charts, and the nurses' notes. The case history for each individual must document that informed consent was obtained prior to participation in the study.
 - iii. Record retention: An investigator must retain required records for a period of 2 years following the date a marketing application is approved

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

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

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

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 subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- g. Follow FDA requirements for inspection of investigator's records and 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

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

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

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

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 subjects under the investigator's care, and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with 21 CFR §50.
 - b. Specific responsibilities of investigators¹²
 - i. Awaiting approval: An investigator may determine whether potential subjects would be interested in participating in an investigation, but must not request the written informed consent of any subject to participate, and must not allow any subject to participate before obtaining IRB and FDA approval.
 - ii. Compliance: An investigator must conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.
 - iii. Supervising device use: An investigator must permit an investigational device to be used only with subjects under the investigator's supervision. An investigator must not supply an investigational device to any person not authorized to receive it.
 - iv. Financial disclosure:
 - 1. A clinical investigator must disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required under 21 CFR §54.
 - 2. The investigator must promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.

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

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

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

- 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 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.

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

- 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 subjects: An investigator must permit authorized FDA employees to inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.
- e. Prepare and submit the following complete, accurate, and timely reports¹⁵
 - i. Unanticipated adverse device effects. An investigator must submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
 - ii. Withdrawal of IRB approval. An investigator must report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
 - iii. Progress. An investigator must submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.
 - iv. Deviations from the investigational plan:
 - 1. An investigator must notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency.
 - 2. Such notice must be given as soon as possible, but in no event later than 5 working days after the emergency occurred.
 - 3. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB also is required.

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

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

- v. Informed consent. If an investigator uses a device without obtaining informed consent, the investigator must report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.
- vi. Final report. An investigator must, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.
- vii. Other. An investigator must, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

Appendix B-3 Additional Requirements for Clinical Trials (ICH-GCP or International Conference on Harmonization Good Clinical Practices)

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 subjects 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 Subjects
 - 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 subjects.
 - 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 hazard to trial subjects, or when the changes involve 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 subjects 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 subjects. Investigators should maintain records that document adequately that the subjects 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 is 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 Subjects
- 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 subjects.
 - b. The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB's approval 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 subjects, 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 subjects 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 subjects, 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 subjects 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 subjects. 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 subjects.

- l. When a clinical trial (therapeutic or non-therapeutic) includes subjects 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 subjects who personally give consent and who sign and date the written informed consent form.
 - n. Non-therapeutic trials may be conducted in subjects 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 subjects who can give informed consent personally; b) the foreseeable risks to the subjects are low; c) the negative impact on the subject's well-being is minimized and low; d) the trial is not prohibited by law; and, e) the approval opinion of the IRB is expressly sought on the inclusion of such subjects, 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. Subjects 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 subjects.
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 subjects by unique code numbers assigned to the trial subjects rather than by the subjects' 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 subjects, should assure appropriate therapy and follow-up for the subjects, 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 B-4 Additional Requirements for Department of Defense (DOD) research

1. When appropriate, research protocols must be reviewed and approved by the IRB prior to the Department of Defense approval. Consult with the Department of Defense funding component to see whether this is a requirement.
2. Employees of the Department of Defense (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. Federal employees while on duty and non-Federal persons may be compensated for blood draws for research up to \$50 for each blood draw. Non-Federal persons may be compensated for research participation other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research.
3. Service members must follow their command policies regarding the requirement to obtain command permission to participate in research involving human subjects while on-duty or off-duty.
4. In considering “minimal risk,” the “ordinarily encountered in daily life or during the performance of routine physical or physiological examinations or tests” must not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain).
5. Components of the Department of Defense might have stricter requirements for research-related injury than the DHHS regulations.
6. There may be specific educational requirements or certification required.
7. Suspension or termination of IRB approval of a DOD-supported research must be promptly (within 30 days) reported to the DOD human research protection officer.
8. When conducting multi-site research, there must be a formal agreement between institutions which specify the roles and responsibilities of each party.
9. Other specific requirements of the Department of Defense (DOD) research be found in the “Additional Requirements for Department of Defense (DOD) Research” section in the IRB’s “WORKSHEET: Additional Federal Criteria (HRP-318).”

Appendix B-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 the Department of Energy (DOE) research be found in the “Additional Requirements for Department of Energy (DOE) Research” section in the IRB’s “WORKSHEET: Additional Federal Criteria (HRP-318).”

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

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

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

- c. A statement that participation is completely voluntary and that the subject may withdraw consent and end participation in the project at any time without penalty or prejudice (the inmate will be returned to regular assignment or activity by staff as soon as practicable).
 - d. A statement regarding the confidentiality of the research information and exceptions to any guarantees of confidentiality required by federal or state law. For example, an investigator may not guarantee confidentiality when the subject indicates intent to commit future criminal conduct or harm himself or herself or someone else, or, if the subject is an inmate, indicates intent to leave the facility without authorization.
 - e. A statement that participation in the research project will have no effect on the inmate subject's release date or parole eligibility.
12. You must have academic preparation or experience in the area of study of the proposed research.
13. The IRB application must include a summary statement, which includes:
- a. Names and current affiliations of the investigators.
 - b. Title of the study.
 - c. Purpose of the study.
 - d. Location of the study.
 - e. Methods to be employed.
 - f. Anticipated results.
 - g. Duration of the study.
 - h. Number of subjects (staff or inmates) required and amount of time required from each.
 - i. Indication of risk or discomfort involved as a result of participation.
14. The IRB application must include a comprehensive statement, which includes:
- a. Review of related literature.
 - b. Detailed description of the research method.
 - c. Significance of anticipated results and their contribution to the advancement of knowledge.
 - d. Specific resources required from the Bureau of Prisons.
 - e. Description of all possible risks, discomforts, and benefits to individual subjects or a class of subjects, and a discussion of the likelihood that the risks and discomforts will actually occur.
 - f. Description of steps taken to minimize any risks.
 - g. Description of physical or administrative procedures to be followed to: Ensure the security of any individually identifiable data that are being collected for the study.
 - h. Destroy research records or remove individual identifiers from those records when the research has been completed.
 - i. Description of any anticipated effects of the research study on institutional programs and operations.
 - j. Relevant research materials such as vitae, endorsements, sample consent statements, questionnaires, and interview schedules.

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

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

1. The project must have a privacy certificate approved by the National Institute of Justice Human Subjects Protection Officer.
2. All investigators and research staff are required to sign employee confidentiality statements, which are maintained by the responsible investigator.
3. The confidentiality statement on the consent document must state that confidentiality can only be broken if the subject reports immediate harm to subjects or others.
4. Under a privacy certificate, investigators and research staff do not have to report child abuse unless the subject signs another consent document to allow child abuse reporting.
5. A copy of all data must be de-identified and sent to the National Archive of Criminal Justice Data, including copies of the informed consent document, data collection instruments, surveys, or other relevant research materials.
6. Other specific requirements of the Department of Justice (DOJ) Research Funded by the National Institute of Justice can be found in the "Additional Requirements for Department of Justice (DOJ) Research" section in the IRB's "WORKSHEET: Additional Federal Criteria (HRP-318)."

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

1. Each school at which the research is conducted must provide an assurance that they comply with the Family Educational Rights and Privacy Act (FERPA) and the Protection of Pupil Rights Amendment (PPRA).
2. Provide a copy of all surveys and instructional material used in the research. Upon request parents of 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 the Department of Education (ED) Research can be found in the “Additional Requirements for Department of Education (ED) Research” section in the IRB’s “WORKSHEET: Additional Federal Criteria (HRP-318).”

¹⁶ Children are persons enrolled in research 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 B-8 Additional Requirements for Environmental Protection Agency (EPA) Research

1. Research conducted, supported, or intended to be submitted to EPA is subject to Environmental Protection Agency Regulations.
2. Intentional exposure of pregnant women or children to any substance is prohibited.
3. Observational research involving pregnant women and fetuses are subject to DHHS Subparts B and D.
4. Research involving children must meet category #1 or #2.
5. Other specific requirements of the Environmental Protection Agency (EPA) Research can be found in the “Additional Requirements for Environmental Protection Agency (EPA) Research and Research Intended to be Submitted to the Environmental Protection Agency” section in the IRB’s “WORKSHEET: Additional Federal Criteria (HRP-318).”