



**Mount  
Sinai**

# **Investigator Manual**

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### ***What is the purpose of this manual?***

The Investigator Manual is designed to guide you through policies and procedures related to the conduct of Human Research that are specific to this organization.

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?***

An algorithm for determining whether an activity is Human Research can be found in the [“WORKSHEET HRP-309: Human Research Determination,”](#) located on the PPHS website. 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 PPHS 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 PPHS review and approval. If you have questions about whether an activity is Human Research, contact the PPHS office who will provide you with a determination. If you wish to have a written determination, provide a written request to the PPHS office.

The document [“HRP-101: 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).

### ***What is the Human Research Protection Program?***

The document [“HRP-101: HUMAN RESEARCH PROTECTION PROGRAM PLAN”](#) describes this organization’s overall plan to protect subjects 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.

### ***What training does my staff and I need to conduct Human Research?***

Investigators and staff will be required to complete the online Collaborative Institutional Training Initiative (CITI) human subjects protection online training program. The CITI site can be accessed at <http://www.citiprogram.org/>. This training is valid for 3 years, after which time a refresher CITI course or additional training must be completed. Further information on this training requirement and others will be available on the PPHS website.

Investigators and staff who are involved in FDA-regulated research will also be required to complete either the online Collaborative Institutional Training Initiative (CITI) Good Clinical Practice (GCP) course, or the Mount Sinai Research Compliance department's "Clinical Research: Are You Doing It Right?" course.

Please note that all members of the research team involved in design, conduct, or reporting of the research are required to complete this training. IRB approval will not be granted for protocols in which members of the research team have not completed human research protections training.

### ***How do I submit new Human Research to the IRB?***

Complete the "[FORM HRP-211: Application for Human Research](#)," attach all requested documents per the instructions, obtain all required signatures, and provide the requested number of copies to the PPHS office. Maintain electronic copies of all information submitted to the PPHS.

### ***How do I complete the "FORM HRP-211: Application for Human Research"?***

Form Header (Basic Protocol Information)

1) Protocol Name

Enter the full protocol name and, where applicable, the protocol code or number in parentheses (such as a cooperative group or sponsored protocol).

2) Principal Investigator

Name the person with overall responsibility for the conduct of the Human Research. There can be only one investigator with this overall responsibility. If the PI is new to the institution or the PPHS application process, or if there has been a change in the PI's contact information, include that information within the other submission materials.

3) Primary Contact Name

Name the person who will receive a copy of all communications in addition to the principal investigator. Leave blank if there is no contact other than the principal investigator. There can only be one contact. If this person is new to institution or the PPHS application process, or if there has been a change in their contact information, mention that within the other submission materials.

4) Contact Info

Provide that person's email and direct phone number in the area provided.

5) Date Revised

Provide the date that the application form is being filled out.

6) Study Number

Provide the study number when known. It may not be known at time of initial submission.

#### Section A: Elements of the Research

Check each applicable item to indicate whether the Human Research involves the following and complete the associated forms:

- a) Use of any external (i.e. non-MSSM) sites at which Human Research activities will be conducted – For example, if you are conducting research in a school, nursing home, or other external facility or site, list it here. Research affiliates such as the Queens Hospital Network, Elmhurst Hospital Network, Jewish Home and Hospital, and Bronx VA are considered external sites.
- b) Use of drugs other than the use of approved drugs in the course of medical practice
- c) Use of a device to evaluate its safety or effectiveness
- d) Use of a HUD to evaluate its safety or effectiveness
- e) Submission of a protocol already approved by the MSSM IRB under a different principal investigator. Your intention is to activate the same protocol at a different site(s) for which you are taking separate and full responsibility.

### Section B: Approvals Required Prior to Initiating Research

Check all additional approvals that are required:

- a) Radiation being used for reasons other than clinical care
- b) Use of materials requiring approval from the Institutional Biosafety Committee. This would include biohazards, toxins, infectious agents (of biological origin or otherwise), recombinant DNA, etc. Check the IBC website for materials that require IBC submission and approval.
- c) Cancer research that requires approval from the Protocol Monitoring & Review Committee. Check with the PR&MC for the kinds of projects that require PR&MC submission and approval.
- d) Investigators or research staff with a significant financial conflict of interest in the research. Refer to the FCOIR website or committee for definitions, disclosure requirements, and management plans (if applicable).
- e) Pathological specimens that require approval from the Pathology department. Check with the Department of Pathology for materials that require submission and approval.
- f) Human embryonic stem cells. Check with the ESCRO committee for materials that require ESCRO submission and approval.
- g) Study of use/outcomes for a product sold to Mount Sinai at full price and sponsored by entity with economic interest in sale of product. Check with the “Registry Committee” for additional information regarding their review and approval process.
- h) Submission required by the Grants and Contracts Office. Check with the GCO regarding their submission requirements
- i) Submission required by the Clinical Trials Budget and Billing Compliance (CTBB). Check with the Office of Clinical Research (OCR) regarding their CTBB checklist, submission requirements, coverage analysis (MCA) and approvals.

### Section C: Funding Sources

List all funding sources. For each, list the associated grant number and Infoed/GCO ID#, if known. Note: modifying funding sources requires that you inform GCO and make appropriate FCOIR disclosures.

### Section D: Reserved

Section E: Names of all research personnel involved in the design, conduct, or reporting of the research

- 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.
- Indicate each person's department(s). If personnel have multiple department appointments, list the department that may be related to the topic of this research first.
- Indicate each person's role in the research.
- If this person is new to institution or the PPHS application process, or if there has been a change in their contact information, submit that information with the other submission materials.
- Check the box if the person will have contact with subjects or access to private identifiable data and whether the person will be involved in the consent process.
- Check the box if the person has fulfilled their PPHS education requirements. The research will not be approved if all individuals have not completed the requirements. Further information regarding the requirements is available in the "What training does my staff and I need to conduct Human Research?" section of this document.
- Indicate the location of "evidence of qualifications". The location may vary by role in the research. Typically investigators submit a copy of their CV or biosketch, and others provide a resume or a summary description of their qualifications.
- Indicate whether the person has a significant financial interest related to the Human Research. The definition of "significant financial interest related to the Human Research" is included on the application and in the institutional Financial Conflict of Interest in Research policies.

Section F: Other Documents

Provide the requested copies of additional documents.

Section G: Principal Investigator signature

Personally sign and date the application.

Section H: Departmental/Designee Approval

Have your department chair or their official designee sign and date the application. Follow any departmental procedures that are required in order to obtain their approval. This signature is in addition to signatures obtained for other institutional requirements (such as GCO submissions).

Note: if the research involves personnel from multiple departments, the Chair of each department represented must sign and date the application. A standalone document "[HRP-211h: Application for Human Research Standalone Chair Signoff Section](#)" is available on the PPHS website for this purpose.

Note: if facilities/resources are required for this Human Research which the listed personnel do not have formal authority to provide (e.g. radiology scanning time), it is the PI's responsibility to obtain permission for these resources prior to the PPHS submission to assure the feasibility of the Human Research.

#### Appendix A: External Site Approvals

If applicable, list any non-MSSM study sites/facilities in which human research activities will be conducted, and provide a contact name and contact information for each site. Indicate whether an authorized representative of the site has granted permission for you to conduct the Human Research and provide evidence of this permission when available. Indicate if the site's IRB will review the Human Research (answer No if the site does not have an IRB). Answer whether the site will request to rely on our IRBs, or another IRB. Research affiliates such as the Queens Hospital Network, Elmhurst Hospital Network, Jewish Home and Hospital, and Bronx VA are considered external sites.

#### Appendix B: Drugs/Biologics

Complete Appendix B for the drug(s) or biologic(s) being used in the Human Research (FDA approved and unapproved). This form does not need to be completed for FDA-approved drugs or biologics whose use in a protocol is totally up to the discretion of an attending physician (not specifically prescribed by the protocol.) Each Appendix B form needs to be signed by the Research Pharmacy. Follow Research Pharmacy policy regarding their submission requirements.

#### Appendix C: Devices

Complete one Appendix C form for each device being evaluated for safety or effectiveness (approved and unapproved). Please obtain any necessary departmental approvals for device use/storage prior to the submission to the PPHS.

### ***How do I write a protocol using the MSSM template?***

Use the "[HRP-503a: Template Protocol](#)" and accompanying "[HRP-503: Template Protocol Instructions](#)" as a starting point for drafting a new protocol, and reference the instructions in italic text for the information the PPHS looks for when reviewing protocols. Here are some key points to remember when developing a protocol:

- The italicized bullet points in the "[HRP-503: Template Protocol Instructions](#)" serve as guidance to investigators when developing a Human Research Protocols for submission to the PPHS. All italicized comments are meant to be deleted prior to submission.
- For any items described in a "sponsor's protocol" or other documents submitted with the application, investigators may simply reference the page numbers of these documents within the protocol template rather than repeat information.
- When writing a protocol, always keep an electronic copy. You will need to modify this copy when making changes to the protocol.
- If you believe your activity may not be Human Research, contact the PPHS office prior to developing your protocol.
- Note that, depending on the nature of your research, certain sections of the protocol template may not be applicable. Indicate this as appropriate by marking "N/A" after each section heading.

### ***How do I activate a protocol at a new MSSM site if it has already been approved by the MSSM IRB for another site?***

In some cases (e.g. multi-site drug trials), the same protocol may be submitted to the IRB by separate principal investigators for separate sites under MSSM jurisdiction. If you are trying to activate a protocol at a new site/sites for which you will serve as the principal investigator, and the MSSM IRB has already approved the protocol for another principal investigator at another site, you may develop and submit a protocol that omits the following sections from the Human Research Protocol template:

- Objectives
- Background
- Inclusion and Exclusion Criteria
- Study Timelines
- Study Endpoints
- Procedures Involved in the Human Research
- Specimen Banking
- Data Management and Confidentiality
- Provisions to Monitor the Data to Ensure the Safety of Subjects
- Withdrawal of Subjects
- Risks to Subjects
- Provisions for Research Related Injury
- Potential Benefits to Subjects
- Multi-Site Human Research (Coordinating Center)

Complete the Human Research Protocol template by describing information specific to the site(s) for which you will serve as Principal Investigator. Do not repeat information in the approved protocol that applies to all site(s).

When submitting the Application for Human Research form and the additional required appendices and documents, you may omit the following when they exist:

- Evaluation instruments and surveys
- Grant application
- Complete sponsor protocol including DHHS-approved protocol (e.g., an NIH-sponsored Cooperative Group Clinical Trial protocol)
- DHHS-approved sample consent document ((e.g., sample consent from an NIH-sponsored Cooperative Group Clinical Trial)
- Current investigator brochure for each investigational drug
- Current package insert for each marketed drug
- Current product information for each investigational device
- If the research is conducted or funded by the Department of Energy, a completed “Checklist for IRBs to Use in Verifying that HS Research Protocols are In Compliance with DOE Requirements”

### ***How do I create a consent document?***

Use the “HRP-502 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 PPHS's "[WORKSHEET HRP-311: Criteria for Approval and Additional Considerations](#)," to ensure that these elements are addressed.

We require that you date the revisions of your consent documents to ensure that you use the most recent version approved by the IRB with prospective subjects, and to fulfill your researcher record-keeping responsibilities.

### ***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 subjects" for the activity to fall under PPHS oversight. Activities that meet neither definition of "research" nor "human Subjects" are not subject to PPHS oversight or review. Review the PPHS office's "[WORKSHEET HRP-309: Human Research Determination](#)" for reference. *Contact the PPHS office in cases where it is unclear whether an activity meets the regulatory definition of Human Research.*
- Exempt: Certain categories of Human Research may be exempt from regulation applicability but still require review and a determination made by someone other than the investigator. Review the PPHS's "[WORKSHEET: Exemption Determination](#)" for reference on the categories of research that may be exempt. If your department has a PPHS-certified Exempt Determiner, that individual is authorized to provide an unofficial exemption determination. Official exempt determinations can only be made by the PPHS office (official determination may be required by an external funder or journal).
- Review Using the Expedited Procedure: Certain categories of non-exempt Human Research may qualify for review that does not require convened IRB review (called an "expedited" procedure). Review the PPHS's "[CHECKLIST HRP-413: 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 an IRB can make when reviewing a protocol?***

An IRB may approve research, require modifications 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.
- Response to PPHS Required to Secure Approval: Made when IRB members require specific affirmations or modifications to a protocol before approval can be finalized.
- Response to PPHS Required to Determine Not Human Subject Research: Made when specific affirmations or modifications to a protocol are required before a determination that a protocol does not involve human subject research can be finalized.

- **Tabled:** Made when the IRB cannot approve the research at a meeting for reasons unrelated to the protocol, such as loss of quorum. When taking this action, the IRB automatically schedules the protocol for a subsequent meeting.
- **Deferred:** Made when the IRB determines that the board is unable to approve a protocol and the IRB suggests modifications the 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 a protocol and the IRB cannot describe modifications the might make the research approvable. When making this motion, the IRB describes its reasons for this decision and gives the investigator an opportunity to respond to the IRB in person or in writing.

### ***How does the IRB decide whether to approve Human Research?***

The criteria for IRB approval can be found in the “WORKSHEET: Exemption Determination” for exempt Human Research and the “CHECKLIST HRP-311: Criteria for Approval and Additional Considerations” for non-exempt Human Research. The latter checklists reference other checklists that might be relevant. All checklists can be found on the IRB Web site.

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

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

### ***What will happen after IRB review?***

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

- **If the IRB has approved the Human Research:** The Human Research may commence once all other organizational approvals have been met. IRB approval for non-exempt research is good for a limited period of time, as noted in the approval letter.
- **If the IRB requires a response to secure approval** and you are agreeable to the modifications or confirmations required, make the requested modifications or confirmations and submit them to the IRB within 30 days using “FORM HRP-214: Response to PPHS” If all requested modifications or confirmations 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 responses will be withdrawn. If you do not accept the requested modifications or confirmations, write up your response and submit it to the IRB within 30 days. If you do not provided additional information or correspondence within 30 days, the IRB will require a complete new protocol submission.
- **If the IRB requires a response to determine that a protocol is not human subject research,** and you are agreeable to the modifications or confirmations required, make the requested modifications or confirmations and submit them to the IRB within 30 days. You may find using “FORM HRP-214: Response to PPHS” helpful. If all requested modifications or confirmations are made, the IRB

will issue a final determination. Research cannot commence until this final determination is received. If you do not respond to the IRB within 30 days, the offer of determination given the requested responses will be withdrawn. If you do not accept the requested modifications or confirmations, 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, the IRB will require a complete new protocol submission.

- If the IRB defers the Human Research: The IRB will provide a statement of the reasons for deferral and may provide suggestions on how to make the study approvable, and will give you an opportunity to respond in writing. In most cases if the IRB's reasons for the deferral are addressed by a subsequent modification, the Human Research can be approved. You may submit a response to the IRB using "FORM HRP-214: Response to PPHS."
- 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 request to address your concerns to the IRB directly at an IRB meeting.

### ***What are my obligations after IRB approval?***

- 1) Do not start Human Research activities until you have the final IRB approval letter. NOTE: If you are in receipt of an "approved pending funding" letter from the IRB, you must take the required action stipulated in the letter before you will receive the final IRB approval letter and be able to begin any Human Research activities.
- 2) Personally conduct or supervise the Human Research.
  - 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 in accordance with the relevant current protocol as approved by the IRB.
  - c) Do not modify the Human Research without prior IRB review and approval unless necessary to eliminate apparent immediate hazards to subjects.
    - i) Report any changes in approved research initiated without prior IRB approval to eliminate apparent immediate hazards to subjects promptly (within 5 days) to the IRB using FORM HRP-224: Reportable New Information
    - ii) The IRB will review this information to determine whether each change was consistent with ensuring the subject's continued welfare
  - d) Protect the rights, safety, and welfare of subjects involved in the research.
- 3) Submit to the IRB:
  - a) Proposed modifications as described in this manual. (See "How do I submit a modification?")
  - b) A continuing review application as requested in the approval letter and as described in this manual. (See "How do I submit continuing review?")
  - c) A final review application when the Human Research is closed. (See "How Do I Close Out a Study?")
- 4) Report any of the information items on the "FORM HRP-224: Reportable New Information" to the IRB within five business days.
- 5) Do not accept or provide payments to professionals in exchange for referrals of potential subjects ("finder's fees.")
- 6) Do not accept payments designed to accelerate recruitment that were tied to the rate or timing of enrollment ("bonus payments.")

- 7) Maintain signed and dated consent documents for three years after completion of the research. Maintain signed and dated HIPAA authorizations and consent documents that include HIPAA authorizations for six years after completion of the research.
- 8) See additional requirements of various federal agencies in Appendix A of this document.

### ***How do I document consent?***

The document “[HRP-091 - SOP - Written Documentation of Consent](#)”, establishes the process to document the informed consent process in writing.

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

The following are some requirements for consent documentation:

- The subject or representative signs and dates the consent document.
- The individual obtaining consent signs and dates the consent document.
- Whenever required by the IRB, the subject’s or representative’s signature is to be witnessed by an individual who signs and dates the consent document.
- For subjects who cannot read, and whenever required by the IRB or the study 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 subjects who cannot provide a signature, refer to the procedures in “[HRP-091 - SOP - Written Documentation of Consent](#).”

### ***How do I submit a modification?***

Complete the “[FORM HRP-213: Modification of Approved Human Research](#),” attach all requested supplements, have the form signed by the individuals listed in the form, and provide the requested number of copies to the PPHS office. Maintain electronic copies of all information submitted to the IRB. Please note that research must continue to be conducted without inclusion of the modification until IRB approval is received.

If the research is determined to be “exempt”, and a proposed modification affects the design and conduct of the research in the approved protocol (including the subjects, sources, or mechanisms of data/material collection), complete the “[FORM HRP-213: Modification of Approved Human Research](#),” attach all requested supplements, and provide the requested number of copies to the PPHS office

### ***How do I submit for a continuing review?***

Complete the “[FORM HRP-212: Continuing/Final Review Progress Report](#),” attach all requested supplements, have the form signed by the individuals listed in the form, and provide the requested number of copies to the PPHS office. Maintain electronic copies of all information submitted to the IRB.

If the continuing review involves modifications to previously approved research, submit those modifications as a separate request for modification using the “[FORM HRP-213: Modification of Approved Human Research](#).”

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

If the approval of Human Research expires all Human Research procedures related to the protocol under review must cease, including recruitment, advertisement, screening, enrollment, consent, interventions, interactions, and collection of private identifiable information. Continuing Human Research procedures is a violation of federal regulations. If current subjects will be harmed by stopping Human Research procedures that are available outside the Human Research context, provide these on a clinical basis as needed to protect current subjects. If current subjects will be harmed by stopping Human Research procedures that are not available outside the Human Research context, immediately contact the IRB chair and provide a written list of the currently enrolled subjects and why they will be harmed by stopping Human Research procedures.

Human research that is determined to be “exempt” does not require continuing review. However, a “FORM HRP-212: Continuing/Final Review Progress Report” should be submitted within 30 days of the completion of the study.

### ***How do I close out a study?***

Complete the “FORM HRP-212: Continuing/Final Review Progress Report,” attach all requested supplements, have the form signed by the individuals listed in the form, and submit the documents to the PPHS office. Maintain electronic copies of all information submitted to the IRB.

If you fail to submit a continuing/final review form to close out Human Research, you will be restricted from submitting new Human Research until the completed application has been received.

If the continuing/final review application 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.

### ***How long do I keep records?***

You are required to comply with Institutional record retention policy as outlined in the FACULTY HANDBOOK.

Under federal regulations, you must maintain your Human Research records, including signed and dated consent documents, for three years after closing out the Human Research. Maintain HIPAA authorizations and other records related to HIPAA compliance for six years.

If you are the sponsor-investigator of an IND or IDE, or if the Human Research is otherwise under the jurisdiction of the FDA, additional requirements for recordkeeping may be involved. Consult with the Compliance Department regarding your situation.

If your Human Research has a financial sponsor, contact the sponsor before disposing of Human Research records.

### ***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 Research Pharmacy immediately to discuss the situation.

See the “WORKSHEET HRP-317: Emergency Use of a Test Article in a Life Threatening Situation” for the regulatory criteria allowing such a use and make sure these 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.

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. Research Pharmacy has a form that they will provide to you to help them make the appropriate determination that the situation meets the criteria for an emergency use. Research Pharmacy also will provide you with a template information sheet to customize for the situation. 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 get additional information and answers to questions?***

This document and the policies and procedures for the Program for Protection of Human Subjects are available on the IRB Web Site at <http://www.mssm.edu/pphs>.

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

- Phone: (212) 824-8200

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 contact the PPHS office, follow the directions in the “HRP-101: HUMAN RESEARCH PROTECTION PROGRAM PLAN” under “Reporting and Management of Concerns.”

## ***Appendix A-1 Additional Requirements for DHHS-Regulated Research<sup>1</sup>***

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.

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<sup>1</sup> <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:<sup>2</sup>
  - 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:<sup>3</sup>
    - i. An investigator, or any person acting on behalf of an investigator, must not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug.
    - ii. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.
    - iii. An investigator must not commercially distribute or test market an investigational new drug.
  - b. Follow FDA requirements for general responsibilities of investigators<sup>4</sup>
    - 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.

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

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

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



- ii. An investigator must, in accordance with the provisions of 21 CFR §50, obtain the informed consent of each human subject to whom the drug is administered, except as provided in 21 CFR §50.23 or §50.24 of this chapter.
- iii. Additional specific responsibilities of clinical investigators are set forth in this part and in 21 CFR §50 and 21 CFR §56.
- c. Follow FDA requirements for control of the investigational drug<sup>5</sup>
  - i. An investigator must administer the drug only to subjects under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator.
  - ii. The investigator must not supply the investigational drug to any person not authorized under this part to receive it.
- d. Follow FDA requirements for investigator recordkeeping and record retention<sup>6</sup>
  - i. Disposition of drug:
    - 1. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects.
    - 2. If the investigation is terminated, suspended, discontinued, or completed, the investigator must return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 21 CFR §312.59.
  - ii. Case histories.
    - 1. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation.
    - 2. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital charts, and the nurses' notes. The case history for each individual must document that informed consent was obtained prior to participation in the study.
  - iii. Record retention: An investigator must retain required records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.
- e. Follow FDA requirements for investigator reports<sup>7</sup>
  - 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:

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

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

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

1. The clinical investigator must provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under 21 CFR §54.
  2. The clinical investigator must promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.
- f. Follow FDA requirements for assurance of IRB review<sup>8</sup>
    - i. An investigator must assure that an IRB that complies with the requirements set forth in 21 CFR §56 will be responsible for the initial and continuing review and approval of the proposed clinical study.
    - ii. The investigator must also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
  - g. Follow FDA requirements for inspection of investigator's records and reports<sup>9</sup>
    - i. An investigator must upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to 312.62.
    - ii. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.
  - h. Follow FDA requirements for handling of controlled substances<sup>10</sup>
    - 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.<sup>11</sup>
      - i. An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with 21 CFR §50.
    - b. Specific responsibilities of investigators<sup>12</sup>
      - 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.

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

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

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

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

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

- ii. Compliance: An investigator must conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.
  - iii. Supervising device use: An investigator must permit an investigational device to be used only with subjects under the investigator's supervision. An investigator must not supply an investigational device to any person not authorized to receive it.
  - iv. Financial disclosure:
    - 1. A clinical investigator must disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required under 21 CFR §54.
    - 2. The investigator must promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.
  - v. Disposing of device: Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator must return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.
- c. Maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:<sup>13</sup>
- 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.

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

- iv. The protocol, with documents showing the dates of and reasons for each deviation from the protocol.
- v. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.
- d. Inspections<sup>14</sup>
  - i. Entry and inspection: A sponsor or an investigator who has authority to grant access must permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept).
  - ii. Records inspection: A sponsor, IRB, or investigator, or any other person acting on behalf of such a person with respect to an investigation, must permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation.
  - iii. Records identifying subjects: An investigator must permit authorized FDA employees to inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.
- e. Prepare and submit the following complete, accurate, and timely reports<sup>15</sup>
  - 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.
  - 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.

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

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

- vi. Final report. An investigator must, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.
- vii. Other. An investigator must, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

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

1. 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 hazards to trial subjects, 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 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 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 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 acceptable 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 acceptable 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 acceptable 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 acceptable 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 acceptable 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 acceptable 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 acceptable representative, and by the person who conducted the informed consent discussion.
- i. If a subject is unable to read or if a legally acceptable 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 acceptable representative, and after the subject or the subject's legally acceptable 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 acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable 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 acceptable 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 acceptable 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 acceptable 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 acceptable 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 acceptable 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 acceptable 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. 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 acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable 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 acceptable 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 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.
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. Determinations of serious or continuing non-compliance, unanticipated problems involving risks to subjects or others, suspension or termination of research must be promptly (no longer than within 30 days) reported to the DoD human research protection officer.
6. The following shall be promptly (no longer than within 30 days) reported to the DoD human research protection officer:
  - a. Significant changes to the research protocol that are approved by the IRB
  - b. The results of the IRB continuing review
  - c. Change of the reviewing IRB
  - d. When the organization is notified by any Federal department, agency or national organization that nay part of the HRPP is under investigation for cause involving a DoD-supported research protocol
7. Other specific requirements of Department of Defense (DOD) research can be found in the “Additional Criterion for Department of Defense (DOD) Research” section in the IRB’s “WORKSHEET HRP-311: Criteria for Approval and Additional Considerations.”

***Appendix A-5 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 HRP-311: Criteria for Approval and Additional Considerations.”

## ***Appendix A-6 Additional Requirements for Department of Energy (DOE) Research***

1. You must report the following promptly (no longer than within 30 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 immediately (within five business days) to the Department of Energy human subject research program manager
  - a. Any compromise of personally identifiable information.
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 HRP-311: Criteria for Approval and Additional Considerations.”

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

1. Each school at which the research is conducted must provide an assurance that they comply with the Family Educational Rights and Privacy Act (FERPA) and the Protection of Pupil Rights Amendment (PPRA).
2. Provide a copy of all surveys and instructional material used in the research. Upon request parents of children<sup>16</sup> involved in the research<sup>17</sup> 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 HRP-311: Criteria for Approval and Additional Considerations.”

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<sup>16</sup> 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.

<sup>17</sup> 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.