



Tufts Medical
Center

Investigator Manual

HRP-103

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1. Introduction

A. Scope

Throughout this document “organization” refers to Tufts University and Tufts Medical Center.

B. Purpose of this manual

This “INVESTIGATOR MANUAL (HRP-103)” 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 *Section 2.A. Human Research Training*.

C. Where to get additional information and answers to questions

This document and the policies and procedures for the Human Research Protection Program are available on the Tufts Health Sciences IRB website at:

<http://www.tufts.edu/central/research/IRB/index.htm>

<http://viceprovost.tufts.edu/HSCIRB/>

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

Tufts Health Sciences Institutional Review Board
 800 Washington Street
 Box 817
 Boston, MA 02111
 (617) 636-7512
 IRBOffice@tuftsmedicalcenter.org

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 IRB Office, follow the directions in the “HUMAN RESEARCH PROTECTION PROGRAM PLAN (HRP-101)” under “Reporting and Management of Concerns.”

D. Human Research

The “HUMAN RESEARCH PROTECTION PROGRAM PLAN (HRP-101)” defines the activities that this organization considers to be “Human Research.” An algorithm for determining whether an activity is Human Research can be found in the “WORKSHEET: Human Research (HRP-310).” Use this document for guidance as to whether an activity meets either the DHHS or FDA definition of Human Research, keeping in mind that the IRB

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makes the ultimate determination in questionable cases as to whether an activity constitutes Human Research subject to IRB oversight.

It is the Investigator’s responsibility to obtain IRB review and approval *before* conducting Human Research. If the research activity is not human research, the IRB will provide you with written documentation of this determination. If you have questions about whether an activity is Human Research, contact the IRB Office.

E. Human Research Protection Program

The document “HUMAN RESEARCH PROTECTION PROGRAM PLAN (HRP-101)” 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.

2. Submitting a Research Study

Refer to the [“New Studies” page](#) on the IRB website for information on the types of review and submission requirements.

A. Communicating with the IRB

Before you begin, whether you are new to the human subject research process, unsure of the submission process, or have questions about specific design elements or potential regulatory requirements, the IRB encourages you to contact the IRB office for consultation early in the research development. The IRB can help you identify strategies to streamline your submission and anticipate and address likely challenges.

The formal IRB records are paper files, so original, typed, signed, paper submissions must be sent or delivered to the IRB office:

Deliver to the IRB Office:

15 Kneeland Street, 1st Floor (Tupper 1)

IRB Interoffice Mail Box:

Box #817

IRB Mailing Address:

Tufts Health Sciences IRB
 800 Washington Street, Box 817
 Boston, MA 02111

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IRB Office Telephone Number:
(617) 636-7512

Contact IRB Office Staff:
<http://viceprovost.tufts.edu/HSCIRB/our-staff/>

For new studies, in addition to the paper original, documents must also be submitted in electronic form (word document or searchable pdf document) via a flash drive). This allows for recommended revisions to be tracked on the actual documents.

You may provide revised documents and responses to IRB comments via e-mail *only* when the IRB Office Staff or IRB Reviewer provide comments and specify that you may provide your response and revised documents via e-mail. Otherwise, submit a paper copy of your response.

When you submit documents to the IRB:

- Submit a cover letter, signed by the PI, that lists the documents being submitted.
- All study documents and especially the Protocol, Informed Consent Form and other participant facing documents, must include a version date, page numbers and clear title. This aids in the IRB review and documentation as well as the research team's version control and organization of study documents.
- Make a copy of the submission for your study records, and make sure you also save each document electronically for future reference.
- File the original correspondence you receive from the IRB in your study records.
- Paper copies of documents should be separated from one another using paper clips, binder clips, staples, or rubber bands (please do not submit as one stack of paper where the documents are not separated from one another, as this could lead to difficulty distinguishing the documents).
- Electronic copies of documents should be in editable (WORD) format when possible (if you do not have the WORD version, please submit PDFs, not scanned copies).
- If submitting electronic documents on a password protected device, please provide the password.

What you can expect once you submit documents to the IRB Office:

- The IRB Office Staff will log each submission received in the IRB Office.
- The IRB Office Staff will triage each submission to the appropriate IRB Office Staff member, and then to the IRB Reviewer or convened IRB meeting.
- The IRB Office Staff will contact the PI and/or Research Coordinator by phone or e-mail if clarification, revisions, or further information is needed.
- The PI will receive a formal "Notice of IRB Comments" letter if your study has been reviewed by the convened IRB.
- You will receive a formal letter of IRB approval. You must receive this formal IRB approval letter before engaging in research activity.

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Tips for quick IRB turnaround time:

- Complete forms accurately and make sure the information in your submission is consistent throughout the submitted documents. This will decrease the amount of “back and forth” and requests from the IRB, which decreases the overall time to final approval.
- Respond to IRB requests in a timely manner.
- Contact the IRB office staff to clarify any aspects of the review process that you do not understand. The IRB wants to engage constructively, and can assist you in responding to queries.
- Ensure the information provided in your responses is also included in the protocol, site-specific appendix, or other applicable study documents. For example, if you provide detailed information about study procedures in your response letter to the IRB, that information should also be included in your study documents.

B. Human Research Training

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

Investigators and staff conducting research involving human subjects must complete the Collaborative Institutional Training Initiative (CITI) human subjects online training program. Investigators and staff conducting research involving no more than minimal risk to subjects must complete the online CITI.

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

Training is valid for a four-year period, after which time the training must be repeated.

All members of the research team involved in the design, conduct, or reporting of the research must complete training. Members of the research team who have not completed human research protections training may not take part in aspects of the research that involve human subjects.

C. Financial Conflict of Interest

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

All research team members (all individuals involved in the design, conduct, or reporting of the research) are required to disclose the financial interests listed in the “Conflict of Interest” sections of IRB forms.

- Initial review submission (new study),
- Continuing review submission, and
- Within 30 days of discovering or acquiring (e.g., through purchase, marriage, or inheritance) a new financial interest.

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

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

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

Contact the Tufts MC Office of the Vice President of Research or the TUHS Office of the Vice Provost for Research with questions about this COI policy.

D. Investigator Protocol

You may use the “[TEMPLATE PROTOCOL \(HRP-503\)](#)” as a starting point for drafting a new Investigator Protocol, and reference the instructions in italic text for the information the IRB looks for when reviewing research. Here are some key points to remember when developing an Investigator Protocol:

- The italicized bullet points in the “[TEMPLATE PROTOCOL \(HRP-503\)](#)” serve as guidance to investigators when developing an Investigator Protocol for submission to the IRB. All italicized comments are meant to be deleted prior to submission.
- When writing an Investigator Protocol, always keep an electronic copy. Maintaining accurate version control is essential. Consider embedding the version control directly in the document file name. You will need to reference specific documents by version/date when submitting or making changes to the Investigator Protocol.
- It is strongly recommended that you speak with the IRB Office Staff about new research projects.
- If you believe your activity may not be Human Research or may be Exempt from regulations, contact the IRB Office before developing your Investigator Protocol.
- Note that, depending on the nature of your research, certain sections of the template may not be applicable to your Investigator Protocol. Indicate this as appropriate.
- If you will enroll any individuals who are members of the following vulnerable populations as subjects in your research, you must indicate this in your inclusion criteria, as the inclusion of subjects in these populations has regulatory implications:
 - Adults unable to provide legally effective consent
 - Individuals who are not yet adults (neonates, children, teenagers)
 - Pregnant women

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- Prisoners
- If you are conducting community-based participatory research, you may contact the IRB Office for information about:
 - Research studies using a community-based participatory research design
 - Use of community advisory boards
 - Use of participant advocates
 - Partnerships with community-based organizations

When you revise a protocol document, you must also update the version date and use the most recent version approved by the IRB.

E. Informed Consent Form (ICF)

Use the [Informed Consent Form \(ICF\) templates](#) to create a consent document.

Note that all informed consent documents must contain all of the required and all additional appropriate elements of informed consent disclosure, unless specifically waived by the IRB. Review the “Long Form of Consent Documentation” section in the IRB’s [“WORKSHEET: Elements of Informed Consent \(HRP-351\)”](#), to ensure that these elements are addressed. If you plan to enroll Non-English speakers, refer to the [Translation of Study Documents](#) and [Tufts short form](#) policies for more information.

When you revise a consent document, you must also update the version date and use the most recent version approved by the IRB.

3. IRB Review

A. Regulatory classifications that research activities may fall under

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

- Not “Human Research”: There are circumstances when the IRB does not require oversight of activities because they do not meet the definition of research (as defined by Department of Health and Human Services (DHHS) and/or Food and Drug Administration (FDA) regulations). At Tufts, the IRB makes not human subjects research determinations. Activities must meet the organizational definition of “Human Research” to fall under IRB oversight. Activities that do not meet this definition are not subject to IRB oversight or review. Per institutional policy, the IRB makes the determination as to whether an activity constitutes Human Research. Refer to the [“Not Human Subject Research”](#) page on the Tufts Health Sciences IRB website for more information.

The IRB uses the WORKSHEET: Human Research (HRP-310) to make these determinations. We also use the WORKSHEET: Engagement Determination (HRP-311) and Engaged Decision Tree (HRP-102) to determine whether the institution is engaged in research.

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Submit to the IRB for a formal determination:

Examples of projects that might not meet the definition of human subjects research, but that should be submitted to the Tufts Health Sciences IRB for a formal determination include:

- [Secondary Data Analysis](#): When specimens or data are reviewed, and individuals' identities cannot be readily ascertained or associated with the information by the investigator. This activity does not involve a Human Subject, defined as a living individual about whom a researcher conducting research obtains data through, an intervention or interaction with the individual, or uses their identifiable private information.
- [Quality Assurance or Quality Improvement \(QA/QI\)](#): Intended to improve or assess internal practices, programs, or systems and are not designed to contribute to generalizable knowledge. Projects initiated for internal purposes in the classroom or institution can fall under this category if the results are not intended to contribute to generalizable knowledge, which refers to information that is intended to be applied outside of the program, process or system being studied.
- [Tufts is not Engaged in Research](#): Activities that would be determined human subject research but does not engage Tufts in human subject research. This determination is made based on the purpose of the research, funding, subject interaction and if a project or any part of it has oversight from another IRB.
- [Research on Decedents](#): Accessing data from individuals that are deceased does not involve a Human Subject, defined as a living individual about whom a researcher conducting research obtains data through. When accessing data on decedents, researchers may not request a decedent's medical history to obtain information about another living person(s), such as a decedent's living relative(s).

Not required to submit to the IRB:

A case report is not research that must be submitted to or approved by the IRB. If an author wants to have a project assessed by the IRB to determine whether it meets the institution's definition of a case report the author may contact the IRB.

- [Case reports](#): Defined as a retrospective analysis of up to three clinical cases that do not meet the Federal Policy for the Protection of Human Subjects definition of Research, which requires an investigation that contributes to generalizable knowledge about a disease or condition.
- [Exempt](#): Certain categories of Human Research may be exempt from regulation, but still require IRB review. It is the responsibility of the organization, not the

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investigator, to determine whether Human Research is exempt from IRB review. Refer to the [“Exempt”](#) page for new studies on the Tufts Health Sciences IRB website for more information.

- Expedited Review: Certain categories of non-exempt Human Research may qualify for review using expedited review procedures, meaning that the research can be reviewed and approved by a single designated IRB Reviewer, rather than the convened IRB. Refer to the [“Expedited and Full Committee”](#) page for new studies page on the Tufts Health Sciences IRB website for more information.
- Review by the Convened IRB: Non-Exempt Human Research that does not qualify for expedited IRB review must be reviewed by the convened IRB (sometimes called “full committee review”). Refer to the [“Expedited and Full Committee”](#) page for new studies on the Tufts Health Sciences IRB website for more information.

Contact the IRB or refer to [OHRP’s Human Subject Regulations Decision Chart](#) for additional guidance on what category your research may fall under.

B. 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.
- Stipulations Required to Secure Approval: Made when IRB members require specific modifications to the research before approval can be granted. Depending on the stipulations, these changes may also require review by the same convened IRB before the IRB grants final approval for the research.
- Tabled: Made when the IRB cannot approve the research at a meeting for reasons unrelated to the research, such as loss of quorum. When taking this action, the IRB automatically schedules the research for review at the next meeting.
- Deferred: Made when the IRB determines that the board is unable to approve research and the IRB suggests modifications that might make the research approvable. When making this motion, the IRB describes its reasons for this decision, describes modifications that would be necessary (or required) to secure approval, and gives the investigator an opportunity to respond to the IRB in person or in writing.
- Disapproval: Made when the convened (full board) 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 convened IRB describes its reasons for this decision and gives the investigator an opportunity to respond to the IRB in person or in writing.

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C. How the IRB decides whether to approve Human Research

The type of review is strictly dependent on the research study design and the nature of the research. Each study is independently assessed to ensure that all criteria for IRB approval have been met.

4. IRB Approval

The IRB will provide the Principal Investigator (PI) with a written determination indicating that the IRB has approved the Human Research, requires stipulations to secure approval, or has disapproved the Human Research.

- If the IRB has approved the Human Research: The Human Research may begin once all other organizational approvals have been met. If the study was approved as Expedited research or reviewed by the convened meeting, the IRB approval is valid for a year (unless stated otherwise). The expiration date will be specified in the approval letter.
- If the IRB requires stipulations to secure approval: Make the requested revisions and submit them to the IRB. Depending on the stipulations, these changes may also require review by the same convened IRB before receiving IRB approval for the research. If all requested changes are made and reviewed by the IRB, the IRB will issue a final approval. Research cannot begin until final approval is granted by the IRB. If you do not agree with the IRB’s recommended revisions, provide your response to the IRB in writing.
- 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 may address your concerns to the IRB directly at an IRB meeting.

5. Post-Approval

A. Investigator’s obligations after IRB approval

Refer to [Investigator Post-Approval Responsibilities](#) on the Tufts Health Sciences IRB website.

B. Documenting consent

Use the signature block approved by the IRB. Complete all items in the signature block, including dates and any applicable check boxes. After all parties have signed, double-check to make sure all the appropriate sections have been completed.

The following are the requirements for long form consent documents:

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

Refer to the following policies on the Tufts Health Sciences IRB website:

- [Short Form Consent Documents and Translations into Commonly Encountered Languages](#)
- [Enrollment of Person who are Unable to Talk, Read, or Write](#)

C. Re-Consent

Under certain circumstances it may be necessary for subjects to re-consent following the presentation of new information. The Principal Investigator (PI) and IRB are to consider the need for re-consent when new information is submitted to the IRB that might affect a subject's willingness to continue to participate in the research study.

The following are among the situations when the IRB may require re-consent:

- The research has changed, or important new information relevant to the subject's continued participation is discovered. Investigators should address whether re-consent is necessary at time of discovering new information, submission of new risk information, or protocol amendment.
- An individual temporarily lost decision-making capacity when initially enrolled in a study approved to enroll subjects with impaired decision-making capacity, or was enrolled in a study conducted in an emergency setting.
- A subject participates in a longitudinal study. If the study is particularly long, re-consenting the subject may be necessary to maintain a subject's understanding of the relevant research activities. The protocol should include a plan for maintaining informed consent when subjects will be followed over long periods of time.
- A minor was enrolled in a study and reaches 18 years of age while participating in the study. The subject would legally be an adult and his/her consent would be required to continue participation in the study. As applicable, consent would also be required for optional tissue banking and genetic testing.

D. Amendments

Refer to the [Amendments](#) page on the Tufts Health Sciences IRB website.

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E. Continuing Review

Refer to the [Continuing Review](#) page on the Tufts Health Sciences IRB website.

F. Closing out a study

Complete the “Form 5: Continuing Review” or submit a letter, signed by the PI, confirming the following is true (or not applicable):

- The protocol is permanently closed to enrollment.
- All subjects enrolled have completed all protocol related interventions and interactions, including interventions and interactions related to collection of long-term follow-up data.
- Identifiable private information about the subjects is no longer being obtained.
- Analysis of private identifiable information is completed. (This can be true even if a statistical center at another site will analyze private identifiable information from subjects enrolled at this site. Private information is individually identifiable when the identity of the subject is or may readily be ascertained by the investigator or associated with the information.) *And* one of the following is true:
 - The remaining study activity is limited to simply maintaining individually identifiable private information without using, studying, or analyzing such information
 - Or*
 - The remaining study activity involves only the analysis of aggregate data sets without individual subject identifiers.

This closure will be acknowledged via email to the PI.

G. Study Re-activation

To reactivate a study that was previously closed out in the IRB, submit a signed written request to the IRB office, along with required continuing review materials (refer to section “Continuing Review”). The IRB office staff will recall any necessary archived materials from off-site storage.

H. Maintaining records

Maintain your Human Research records, including signed and dated ICFs (including HIPAA authorizations, as applicable), as follows:

- Sponsored Research: An investigator will be responsible for maintaining research records as agreed to in the clinical trial agreement with the study sponsor and in accordance with applicable federal and state law regarding record retention.
- Investigational Drugs: In accordance with 21 CFR 312.57(c) an investigator, or sponsor is to retain the records and reports required by Subpart D of the section for 2 years after a marketing application is approved for the drug; or, if an application is

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not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.¹

- **Investigational Devices:** In accordance with 21 CFR 812.140 an investigator, or sponsor, is to maintain the records required by Subpart G of the section during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is closed or completed, or the date that the records are no longer required for purposes of supporting a pre-market approval application or a notice of completion of a product development protocol.²
- **Other:** In all other studies that do not have a clinical trial agreement, or are not regulated by the FDA, the PI will be required to maintain research records for 7 years after s/he has closed the study with the IRB.

Upon request, a PI will be permitted access to IRB study files. Access will be under the supervision of the IRB office staff. A PI may designate a study team member to access the IRB study file by providing signed written notification/authorization to the IRB office. This written notification/authorization should specify the reason the PI requires access to the IRB study file. The IRB office will document access to the IRB study file. The written authorization from the PI will also be retained in the IRB file.

Only materials submitted by the research team may be photocopied. Official correspondence from the IRB to the PI may also be photocopied. However, IRB reviews, IRB intra-office communications (*e.g.* Memorandum or Note to File), and IRB meeting minutes may not be photocopied without the written and signed authorization of the IRB Chair.

I. Certificate of Confidentiality

A Certificate of Confidentiality protects identifiable research information from forced disclosure in any civil, criminal, administrative, legislative, or other proceeding, whether federal, state, or local. On a case-by-case basis, the IRB will assess whether a Certificate of Confidentiality is needed as a condition of approval in accordance with federal guidance. Such a requirement will be documented by the IRB and will be communicated to the PI. If a Certificate of Confidentiality is obtained, the NIH recommended consent language is to be included in the ICF.

Please refer to the [National Institutes of Health Office of Extramural Research, Certificate of Confidentiality Kiosk](#) for additional information.

J. Research-related Radiation

All X-rays, including Computed Tomography (CT) scan, bone densitometry, mammography, all nuclear medicine procedures, and all radiation therapy procedures, whether they use radioactive sources or external beam (accelerators) emit ionizing radiation.

¹ <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>

² <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>

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When subjects will be exposed to ionizing radiation for research purposes, a [Form 4](#) for radiation is required. The Form 4 must be reviewed and approved by the institutional Radiation Safety Officer before final IRB approval is granted. The Radiation Safety Officer will review the ICF language describing the radiation exposure. Please also refer to the [ICF templates](#) for recommended language and the [Typical Exposure Document](#) for information on the whole body radiation doses from common medical imaging procedures, including their related increase in lifetime cancer risk and the period of natural background radiation that delivers the equivalent radiation dose.

Neither Magnetic Resonance Imaging (MRI) nor ultrasound imaging involves ionizing radiation.

K. Emergency Use

Contact the IRB right away if you need to use an approved drug, biologic, or device and there is no time for IRB review. Refer to the [Emergency Use](#) page on the Tufts Health Sciences IRB website for instructions and further information.

L. Massachusetts Controlled Substances Researcher Registration

Pursuant to Massachusetts General Law [[M.G.L. Chapter 94C, §7](#)], all investigators conducting human subject research involving investigational and/or approved drugs for new indications must register annually with the Massachusetts Department of Public Health (DPH).

Tufts Medical Center and Tufts University have an agreement with the Massachusetts DPH that provides for only the Department Chair or Division Chief to have a valid Controlled Substances Researcher Registration. This registration extends to all the faculty members organized within a registered department.

The IRB office processes applications for Chairs/Chiefs. The Chairs/Chief shall be responsible for completing the necessary Massachusetts DPH form accurately. The original Massachusetts Controlled Substances Researcher Registration is forwarded to each registered Department Chair/Chief, with a copy maintained on file in the IRB office.

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Appendix A-1 ***Additional Requirements for DHHS-Regulated Research³***

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.

³ <http://www.hhs.gov/ohrp/policy/subjectwithdrawal.html>

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

1. When a subject withdraws from a study:⁴
 - 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 ICF). 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:⁵
 - 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.

⁴ <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126489.pdf>

⁵ <http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.7>

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- iii. An investigator must not commercially distribute or test market an investigational new drug.
- b. Follow FDA requirements for general responsibilities of investigators⁶
 - 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 drug⁷
 - 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 retention⁸
 - 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 ICFs 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.

⁶ <http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.60>

⁷ <http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.61>

⁸ <http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.62>

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- 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 reports⁹
 - 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 review¹⁰
 - 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 reports¹¹
 - 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.

⁹ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.64>

¹⁰ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.66>

¹¹ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.68>

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- 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 substances¹²
 - 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.¹³
 - 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 investigators¹⁴
 - 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.

¹² <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.69>

¹³ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.100>

¹⁴ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.110>

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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:¹⁵
 - 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 ICFs 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.

¹⁵ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.140>

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- 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. Inspections¹⁶
 - 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 reports¹⁷
 - 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

¹⁶ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.145>

¹⁷ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.150>

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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.
- 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.

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

1. Investigator's Qualifications and Agreements
 - a. The clinical trial should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practice and the applicable regulatory requirements.
 - b. 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.
 - c. 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.
 - d. The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.
 - e. The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authorities.
 - f. 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.

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- 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 ICF, ICF 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

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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 ICF and any other written information to be provided to subjects.
 - b. The written ICF 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 ICF, 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 ICF, should contain any language that causes the subject or the subject's

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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 ICF, 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 ICF 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 ICF 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 ICF, the witness should sign and personally date the ICF. By signing the ICF, the witness attests that the information in the ICF 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 ICF 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.

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- 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 ICF, 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 ICF 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 ICF 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

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understanding and, if capable, the subject should sign and personally date the written informed consent.

- m. Except as described above, 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 ICF.
 - 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

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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:

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- 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.

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

1. When appropriate, research protocols must be reviewed and approved by the IRB prior to the 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.
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. Components of the Department of Defense might have stricter requirements for research-related injury than the DHHS regulations.
5. There may be specific educational requirements or certification required.
6. When assessing whether to support or collaborate with this institution for research involving human subjects, the Department of Defense may evaluate this institution's education and training policies to ensure the personnel are qualified to perform the research.
7. When research involves U.S. military personnel, policies and procedures require limitations on dual compensation:
 - a. Prohibit an individual from receiving pay or compensation for research during duty hours.
 - b. An individual may be compensated for research if the participant is involved in the research when not on duty.
 - c. Federal employees while on duty and non-Federal persons may be compensated for blood draws for research up to \$50 for each blood draw.
 - d. Non-Federal persons may be compensated for research participating other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research.
8. Other specific requirements of the Department of Defense research be found in the "Additional Requirements for Department of Defense (DOD) Research" section in the IRB's "WORKSHEET: Additional Federal Criteria (HRP-318)."

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

1. You must report the following within ten business days to the Department of Energy human subject research program manager
 - a. Any significant adverse events, unanticipated risks; and complaints about the research, with a description of any corrective actions taken or to be taken.
 - b. Any suspension or termination of IRB approval of research.
 - c. Any significant non-compliance with HRPP procedures or other requirements.
2. You must report the following within three business days to the Department of Energy human subject research program manager
 - a. Any compromise of personally identifiable information must be reported immediately.
3. Other specific requirements of 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).”

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

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

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

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

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

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

1. The project must have a privacy certificate approved by the National Institute of Justice Human Subjects Protection Officer.
2. All investigators and research staff are required to sign employee confidentiality statements, which are maintained by the responsible investigator.
3. The confidentiality statement on the consent document must state that confidentiality can only be broken if the subject reports immediate harm to subjects or others.
4. Under a privacy certificate, investigators and research staff do not have to report child abuse unless the subject signs another consent document to allow child abuse reporting.
5. A copy of all data must be de-identified and sent to the National Archive of Criminal Justice Data, including copies of the informed consent document, data collection instruments, surveys, or other relevant research materials.
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).”

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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 children¹⁸ involved in the research¹⁹ 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).”

¹⁸ 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.

¹⁹ 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.

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

1. Research conducted, supported, or intended to be submitted to EPA is subject to Environmental Protection Agency Regulations.
2. Intentional exposure of pregnant women or children to any substance is prohibited.
3. Observational research involving pregnant women and fetuses are subject to additional DHHS requirements for research involving pregnant women (45 CFR §46 Subpart B) and additional DHHS requirements for research involving children (45 CFR §46 Subpart D.)
4. Research involving children must meet category #1 or #2.
 - 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).”