



**University of California Davis**

# **Investigator Manual**

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## **Scope**

Throughout this document “Institution” refers to University of California Davis.

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

This document “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 Institution. This document discusses the mechanics of working with the IRB and Human Research Protection Program and is not meant to be a repeat of required training.

General information regarding Human Research protections and relevant federal regulations and guidance is incorporated into the required human protections training. For additional information see [What Training do my staff and I need to conduct human subject research?](#)

### ***What is Human Research?***

The “HUMAN RESEARCH PROTECTION PROGRAM PLAN (HRP-101)” defines the activities that this Institution considers to be “Human Research.” An algorithm for determining whether an activity is Human Research can be found in the “[WORKSHEET: HUMAN RESEARCH DETERMINATION \(HRP-310\)](#),” located in the Policies, Procedures and Regulations section of the [IRB Website](#). Use this document or information on the [IRB Administration](#) website for guidance as to whether an activity meets either the DHHS or FDA definition of Human Research, keeping in mind that the IRB makes the ultimate determination in questionable cases as to whether an activity constitutes Human Research subject to IRB oversight.

You are responsible for not conducting Human Research without prior IRB review and approval (or an Institutional determination of exempt Human Research). If you have questions about whether an activity is Human Research, contact the IRB Office. If you wish to obtain a determination letter from the IRB, submit your project through IRBNet for review.

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

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

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

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### ***Who is eligible to be a Principal Investigator?***

This Institution applies UC Davis Policy and Procedure Manual: Chapter 230, Sponsored Programs: Section 02, “[Elegibility to Undertake Sponsored Research](#)” to all sponsored Human Research.. In some instances, investigators will be granted an exception to this policy. Additional information on exceptions can be found at <http://research.ucdavis.edu/wp-content/uploads/Form-105-A-Request-for-Exception-to-Policy-on-Eligibility-to-Submit-Proposals.pdf>.

When UC Davis is engaged in human research the New Project must include a completed [FORM: ADMINISTRATIVE APPROVAL \(HRP-226\)](#) signed by the Department Chair, Dean or Director indicating approval to conduct the research.

### ***May a student or medical resident be a Principal Investigator?***

This Institution allows students or medical residents to act as Principal Investigators in human subject research. They are required to obtain a Faculty Advisor to oversee, guide, and sign off on their research. The Faculty Advisor must be listed on the [FORM: ADMINISTRATIVE APPROVAL \(HRP-226\)](#) and must use the IRBNet “Sign this Package” feature to electronically sign the New Project submission package. HRP-226 must also be signed by the Department Chair or Dean. The Faculty Advisor is required to be listed as part of the research personnel (staff) of the study, and to complete a human subject research online training course. Additional information on the requirements for Residents to act as a principal investigator can be found at <http://www.ucdmc.ucdavis.edu/medresearch/medsp/pi.html>.

### ***May UC Davis researchers include research personnel, who are not faculty, students, or employees of UC Davis, on their researcher?***

UC Davis Investigators and researchers who wish to include research personnel who are **not** a faculty member, student, or employee of UC Davis must contact the [UC Davis IRB Administration Reliance Group](#) in writing before allowing the research personnel to engage in human subject research activities.

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

This section describes the training requirements imposed by the IRB. You may have additional training imposed by other federal, state, or University policies. Any additional requirements will be directed by the funding agency, Sponsored Programs, Legal Affairs, Compliance, Contracts, your department, and/or the IRB Administration.

Investigators, staff, and faculty advisors are required to complete human subject research protection training prior to engaging in human subject research activities. Training should be completed before submitting an application for IRB review when initiating a new study, or prior to engaging in research activities, including access and analysis of private identifiable data, when joining an active research project. It is the

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responsibility of the Principal Investigator to ensure all research staff have completed all necessary training before engaging in research activities. The following personnel must complete training:

- Principal Investigators and Co-Investigators
- Research staff listed on the research personnel list
- Individuals who obtain informed consent from prospective participants in research
- Individuals named as a contact person in the informed consent and recruitment materials for research
- Faculty Advisors/Faculty Sponsors

### Basic Human Research Protections Training

#### Minimal Risk Research

Investigators and staff involved in research that poses no more than minimal risk to subjects may complete any one of the following to meet the basic human research protections training requirement:

- CITI Basic course for Biomedical Researchers and staff; or
- CITI Basic course for Social and Behavioral Researchers and staff

#### Greater than Minimal Risk Research

Investigators and staff involved in research that poses more than minimal risk must complete any one of the following to meet the basic human research protections training requirement:

- CITI Basic course for Biomedical Researchers and staff; or
- CITI Basic course for Social and Behavioral Researchers and staff

#### Good Clinical Practice (GCP) Training

Investigators and staff involved in a clinical investigation or an NIH-funded clinical trial are required to take GCP training in addition to basic human research protections training.

Investigators and staff involved in a clinical investigation under FDA jurisdiction must complete one of the following:

- CITI GCP for Clinical Trials with Investigational Drugs and Biologics (ICH Focus), or
- CITI GCP for Clinical Trials with Investigational Medical Devices.

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If your research involves both investigational drugs and devices, select the training that applies to the majority of your research.

Investigators and staff involved in an NIH-funded clinical trial not subject to FDA jurisdiction you may complete the one of CITI training listed above or either of the following:

- CITI GCP – Social and Behavioral Research Best Practices for Clinical Research; or
- NIH Good Clinical Practice. Offered through the UC Davis Learning Management System, this training focuses on GCP for social and behavioral clinical trials. Once you log into LMS search “NIH” to locate the course.

### Training Certification Period

Training is valid for a three-year period. Investigators and staff must renew their training certification before it expires by taking either a refresher course or retaking the full course. Members of the research team who have not completed human subject research protection training may not take part in aspects of the research that involve human subjects or their private identifiable data. IRB staff assess whether investigators and co-investigators meet applicable training requirements when reviewing submissions for initial review, continuing review and research modifications. Investigators are required to monitor training for all research staff and attest that required training is completed when submitting for initial review, continuing review and research modifications. Investigators and research staff must cease all human subject research activities when training requirements are not met.

If you are involved in the conduct, oversight or management of an NIH funded clinical trial, you are required to be trained in Good Clinical Practice (GCP), consistent with principles of the International Conference on Harmonisation (ICH) E6 (R2). If you fail to maintain the training, you may lose your funding. This requirement applies to investigators and research staff.

### ***What financial interests do my staff and I need to disclose to conduct Human Research?***

Federal regulations require the IRB to review related financial interests (RFIs) to determine whether the relationship could result in bias which could affect the rights and welfare of research subjects and integrity of the research data. Investigators must report all RFIs to the IRB as outlined in [HRP-055 Financial Conflicts of Interest](#).

Investigators must also report RFI's to the UC Davis Conflict of Interest Committee and follow the institution's policies on financial interests in research described by the UC Davis Policy and

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Procedure Manual (PPM) under “Individual Conflicts of Interest Involving Research (230-05)” and/or “Public Health Service Regulations on Objectivity in Research (230-07),” and also in the University of California’s policy under “Disclosure of Financial Interests & Management of Conflicts of Interest, Public Health Service Research Awards (UC-RG-12-0133).”

All individuals involved in the design, conduct, or reporting of research are required to disclose whether they have any RFI as listed in the “Related Financial Interest” section of the “INITIAL REVIEW APPLICATION.” If a new RFI arises, information about the new relationship must be reported within 30 days of acquiring the interest.

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

The UC Davis IRB uses an electronic database called [IRBNet](#). This system provides the research community with electronic protocol management, online submission, and a suite of tools for researchers and IRB staff. IRBNet is hosted at a secure, enterprise-class data center that supports and meets the strict requirements of federal regulations<sup>1</sup>.

Complete the electronic “[INITIAL REVIEW APPLICATION](#),” and upload all requested supplemental documents, including “[FORM: ADMINISTRATIVE APPROVAL \(HRP-226\)](#).” The completed HRP 226, must be signed by the Department Chair or Dean. Check your department policy to determine who should sign the document. The Chair or Dean may physically sign the HRP 226 or electronically sign the package.

- The Principal Investigator is qualified by education, training and experience to personally conduct and/or supervise the research described in the protocol.
- The Principal Investigator has completed all applicable institutional credentialing processes to conduct this research.
- The Principal Investigator has sufficient resources to carry out this research as proposed.
- The protocol is scientifically valid and employs research procedures which are consistent with sound research design.
- The Principal Investigator will conduct the protocol in accordance with requirements in the INVESTIGATOR MANUAL (HRP-103) listed in the section, “[What are my obligations after IRB approval?](#)”

The Principal Investigator and Faculty Advisor (if applicable) must [electronically sign](#) the Initial Review package before the completed packet is submitted to the IRB Administration. Maintain electronic copies of all information submitted to the IRB in case revisions are required.

Before submitting the research for initial review, you must determine whether any member of the research staff has a financial interest related to the research. If “yes”, you must report specific

<sup>1</sup> [21 CFR Part 11, Electronic Records; Electronic Signatures – Scope and Application](#)

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information about the related financial information as described in the section above, “[What financial interests do my staff and I need to disclose to conduct Human Research?](#)”

You must also ensure that every member of the research team who has interactions with participants, intervenes with participants, obtains consent or accesses identifiable private information for research purposes has completed the [required training](#) and received training on the procedures that s/he will conduct for this project.

IRB Administration will screen your submission and direct it through the proper level of review. Some submissions will be reviewed by a designated reviewer (expedited review) and other submissions will require review by a Committee. There are four IRB Committees at UC Davis: Biomedical Committee A, Biomedical Committee B, Social and Behavioral Committee C, and Fast Track Committee D. For additional information, including the schedule of meeting dates, please visit <http://research.ucdavis.edu/policiescompliance/irb-admin/researchers/about-the-committees/>

### ***Will UC Davis IRB Review Research on behalf of another Institution or Investigator?***

UC Davis will review research on behalf of another institution when all requirements for the review are met. One important requirement is to ensure a reliance agreement (explained below) is in place between the external institution and UC Davis. Other requirements for relying on an external IRB can be found at [HRP-059 IRB Reliance When UC Davis is the IRB of Record](#).

Soon, federal funding agencies and departments will require institutions to use a single IRB (sIRB) to review all domestic sites participating in a multisite study. UC Davis will act as a sIRB for these studies upon request. However, review of multisite studies will take planning and coordination, and the costs associated with IRB review of external sites must be included in the budget.

Please notify the UC Davis Reliance Coordinator at [hs-IRBReliance@ucdavis.edu](mailto:hs-IRBReliance@ucdavis.edu) as early in the planning process as possible if you plan to be the lead PI for a federally funded multi-site study.

### ***Will UC Davis rely on an external IRB for review of research conducted by UC Davis faculty, students or staff?***

UC Davis will rely on an external IRB when all requirements are met. A reliance agreement (explained below) between the reviewing IRB and UC Davis must be in place. For information about additional requirements, refer to in [HRP-058 SOP: IRB Reliance When UC Davis Relies on an External IRB](#). Additional information can be found in [HRP-442 CHECKLIST: External IRB review of UC Davis Human Subject Research](#).



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Whenever an investigator from UC Davis relies on an external IRB, s/he must submit an abbreviated application through IRBNet and obtain all ancillary reviews such as Radiation Safety, Conflict of Interest and Biosafety Committee review

During the conduct of the research, UC Davis investigators must comply with the external IRB's requirements for submissions and reporting non-compliance and unanticipated problems involving risks to subjects or others. Investigators and research staff must obtain information about the external IRB's requirements before starting the study.

### ***What is a reliance agreement?***

A reliance agreement is a formal written agreement outlining the role and responsibilities of the reviewing IRB and relying institution/investigator. A reliance agreement is required whenever an external institution relies on UC Davis for review of human subject research and when an external IRB reviews human subject research for a UC Davis investigator.

The agreement may be an Individual Investigator Agreement (IIA) or an IRB Authorization Agreement (IAA). UC Davis has several agreements in place including the UC Reliance Registry, Neuronext, IRBChoice and the NCATS National SmartIRB agreement. If you are planning to participate in collaborative or multi-site research, and believe an IRB authorization agreement will be required, contact [HS-IRBReliance@ucdavis.edu](mailto:HS-IRBReliance@ucdavis.edu) to see if an agreement is in place. If no agreement is in place, IRB Administration will work with you and the participating institution(s) to obtain the required agreement(s).

Investigators and research staff are not authorized to sign IRB reliance agreements. Each agreement must be signed by the Institutional Official (or designee) of the relying site and by the Institutional Official (or designee) of the reviewing site. If you receive an authorization agreement from an external institution, you should send it to [HS-IRBReliance@ucdavis.edu](mailto:HS-IRBReliance@ucdavis.edu). IRB Administration will determine whether the reliance can take place and will work with the external institution to complete the agreement. For more information, contact the UC Reliance Coordinator at [hs-IRBReliance@ucdavis.edu](mailto:hs-IRBReliance@ucdavis.edu).

### ***How do I write an Investigator Protocol?***

Use the "[INITIAL REVIEW APPLICATION](#)" within IRBNet and reference the instructions in the "[IRBNET USER MANUAL: INITIAL REVIEW APPLICATION](#)". In addition to the "[INITIAL REVIEW APPLICATION](#)", if you do not have a sponsor protocol, use the "[TEMPLATE PROTOCOL HRP 503](#)".

If your research involves only review of data or specimens, you should use the [RECORD/DATA/SPECIMEN REVIEW TEMPLATE HRP 503](#). If your research involves only surveys, interviews or focus groups, you should use the "[SURVEYS/INTERVIEWS AND/OR FOCUS GROUPS REVIEW TEMPLATE HRP 503](#)".

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Here are some key points to remember when developing an Investigator Protocol:

- The italicized bullet points in the protocol templates serve as guidance to investigators when developing an Investigator Protocol for submission to the IRB. Please delete all italicized comments prior to submission.
- Certain sections of the template may not be applicable to your project. Please mark inapplicable sections with “N/A”.
- In some instances a project may appear to be human subject research when it does not meet the regulatory definitions of human subject research. More information can be found on the [IRB Website](#). If you believe your activity may not be Human Research, read the information on our website. If you need a formal determination from the IRB that your project is not human research, create and submit a new project in IRBNet.
- You may not include any individuals of the following populations as subjects in your research unless you indicate in your application the populations will be included.
  - Adults who lack the capacity to provide legally effective consent
  - Individuals who are not yet adults (infants, children, teenagers)
  - Pregnant women
  - Prisoners
- If you are conducting community-based participatory research, you may contact the IRB Administration 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 Institutions

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

Use one of the “[TEMPLATE CONSENT DOCUMENT \(HRP-502\)](#)” to create a consent document.

Note that long form consent documents and summaries for short form consent documents must contain all of the required and additional appropriate elements of informed consent disclosure. Review the “Long Form of Consent Documentation” section in the IRB’s “[WORKSHEET: CRITERIA FOR APPROVAL AND ADDITIONAL CONSIDERATIONS \(HRP-314\)](#),” to ensure that these elements are addressed. When using the short form of consent documentation the appropriate signature block should be used. The short form of consent (HRP-507) is only intended for use in biomedical research when a potential non-English speaking participant is identified. The short form is available in several languages on the [IRB Website](#).

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If your research study meets the requirements for an [exemption](#), you may use an abbreviated process for obtaining consent. Consent can be verbal, but you must provide the following information to participants through an information sheet or written script:

- The subject is being asked to participate in a research study;
- A description of the procedure(s) the participant will be asked to complete;
- Participation is voluntary; and
- The investigator’s name and contact information.

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

### ***What are the different requirements for each level of IRB review?***

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

- Not “Human Research”: Activities must meet the Institutional definition of “Human Research” to fall under IRB oversight. Activities that do not meet this definition are not subject to IRB oversight or review. Review the IRB Office’s “[WORKSHEET: HUMAN RESEARCH \(HRP-310\)](#)” or the [IRB Website](#) for reference.
- Exempt: Certain categories of Human Research may be exempt from regulation but require IRB review. It is the responsibility of the Institution, not the investigator, to determine whether Human Research is exempt from IRB review. Review the IRB Administration’s “[WORKSHEET: EXEMPTION DETERMINATION \(HRP-312\)](#)” or the [IRB Website](#) for information on the categories of research that may be exempt.
- Review Using the Expedited Procedure: Certain categories of non-exempt Human Research may qualify for review using the expedited procedure, meaning that the project may be approved by a single designated IRB reviewer, rather than the convened board. Review the IRB Administration’s “[WORKSHEET: ELIGIBILITY FOR REVIEW USING THE EXPEDITED PROCEDURE \(HRP-313\)](#)” for reference on the categories of research that may be reviewed using the expedited procedure.
- Review by the Convened IRB: Non-Exempt Human Research that does not qualify for review using the expedited procedure must be reviewed by the convened IRB.

### ***What are the decisions the IRB can make when reviewing proposed research?***

The IRB may approve research, require modifications to the research to secure approval, table research, or disapprove research:

- Approval: Made when all criteria for approval are met. See “How does the IRB decide whether to approve Human Research?” below.
- Modifications Required to Secure Approval: Made when IRB members require specific modifications to the research before approval can be finalized.

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- **Deferred:** Made when the IRB determines that the board is unable to approve the research and the IRB suggests modifications that might make the research approvable. When making this motion, the IRB describes its reasons for this decision, describes modifications that might make the research approvable, and gives the investigator an opportunity to respond to the IRB in person or in writing.
- **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.
- **Disapproval:** Made when the IRB determines that it is unable to approve research 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 \(HRP-312\)](#)” for exempt Human Research and the “[WORKSHEET: CRITERIA FOR APPROVAL AND ADDITIONAL CONSIDERATIONS \(HRP-314\)](#)” for non-exempt Human Research. The latter worksheet references other checklists that might be relevant. All checklists and worksheets can be found on the [IRB Administration Website](#).

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 Investigator Protocol in a way that addresses the criteria for approval. Please do not include the checklists in your submission.

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

The IRB will provide you with a notification indicating one of the following determinations:

- The submission is not research involving human subjects (NHSR)
- The research is exempt from the requirement for IRB review
- The IRB approved the Human Research,
- Modifications to the submission are required to secure approval of the Human Research;  
or
- The IRB disapproved the Human Research.

If a submission is not fully approved and the IRB **requires modifications** to secure approval and you accept the modifications, make the requested modifications and submit them to the IRB ([SOP: INCOMING ITEMS DIRECTED TO THE IRB \[HRP-020\]](#)). If all requested modifications are made, the IRB will issue a final approval per “[SOP: POST-REVIEW \(HRP-052\)](#).” Research cannot commence until this final approval is received. If you do not accept the modifications, write up your response and submit it to the IRB. The response will be placed on

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the next available agenda for review by a convened IRB ([SOP: PRE-REVIEW \[HRP-021\]](#) and [SOP: IRB MEETING CONDUCT \[HRP-041\]](#)).

If the IRB **defers** the Human Research, the letter will include the reasons for deferral, suggestions to make the study approvable, and give you an opportunity to respond in person or in writing. Address the suggestions and submit the response to the IRB ([SOP: INCOMING ITEMS DIRECTED TO THE IRB \[HRP-020\]](#)). The response will be placed on the next available agenda for review by a convened IRB ([SOP: PRE-REVIEW \[HRP-021\]](#) and [SOP: IRB MEETING CONDUCT \[HRP-041\]](#)). In most cases, if the IRB's reasons for the deferral are addressed in the modifications, the Human Research can be approved ([SOP: POST-REVIEW \[HRP-052\]](#)).

If the IRB **disapproves** the Human Research, the letter will include a statement of the reasons for disapproval and give you an opportunity to respond in writing.

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

If your submission is approved, determined exempt or NHSR, you may start the research when all other required institutional approvals have been obtained.

### ***Will IRB approval expire?***

If you receive a notification that the submission is NHSR or exempt, the project will not expire.

If the research goes through expedited or full committee review you will receive a notification when the research is approved, and an Approval Letter will be published in IRBNet. The Approval Letter and the IRBNet Project Overview page will state the date IRB approval of the research expires. This date is based on several factors, including the risk of the research.

Research involving greater than minimal risk will usually be granted a one-year approval; however, in some instances, these studies may receive an approval term that is less than one-year.

Research that meets the requirements below will usually be granted a 10-year approval:

- This research involves no more than minimal risk.
- This research does not receive any federal or state government funding or funding from a private funder who requires annual review per contract.
- This research is not subject to FDA jurisdiction.
- This research does not include prisoners as participants.
- This research is not subject to SCRO oversight.
- This research is not subject to oversight by the Research Advisory Panel of California (RAP of C).
- This research does not involve identifiable information held by the State of California Department or Agency.
- No personnel involved in the design, conduct, or reporting of this research have a new unreported related financial interest (RFI) in this study..

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At least 45-days before IRB approval of the research expires, you must submit information to the IRB requesting either continuing review or study closure. The requirements for continuing review and study closure are found below in the section, “How do I submit a continuing review?”

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

- 1) Do not start Human Research activities until you have the final IRB approval letter.
- 2) Do not start Human Research activities until you have obtained all other required institutional approvals, including approvals of departments or divisions that require approval prior to commencing research that involves their resources. For instance, at UC Davis when an investigational drug or biologic is involved, the UC Davis PI is required to defer responsibility for accounting, storage, dispensing, etc. to the UC Davis Health Investigational Drug Services (IDS) Pharmacy.
- 3) Ensure that there are adequate resources to carry out the research safely. This includes, but is not limited to, sufficient investigator time, appropriately qualified research team members, equipment, and space.
- 4) Ensure that Research Staff are qualified (e.g., including but not limited to appropriate training, education, expertise, credentials, protocol requirements and, when relevant, privileges) to perform procedures and duties assigned to them during the study.
- 5) Update the appropriate IRB office with any changes to the list of study personnel (other than PI and Co-PI) at time of continuing review, if applicable or annually. To change the PI and/or Co-PI, a modification must be submitted and approved by the UC Davis IRB before the new PI and/or CO-PI can engage in human research activities.
- 6) 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) Protect the rights, safety, and welfare of subjects involved in the research.
- 7) Report changes in funding as soon as you receive notification of an award.
- 8) Do not make any modifications to approved research without first obtaining prior approval from the IRB unless the modification is necessary to protect participants from imminent harm. To request approval of a modification, see “[How do I submit a modification?](#)”)
- 9) Respond promptly to notifications from the IRB.
- 10) When required, submit a continuing review application to the IRB. The expiration date for your research can be found in the approval letter. See “[How do I submit a continuing review?](#)” for instructions for submitting a continuing review report.
- 11) Submit a continuing review application when the Human Research is closed. See “[How do I close out a study?](#)” for more information.
- 12) Report to the IRB using “[FORM: REPORTABLE NEW INFORMATION \(HRP-214\)](#),” any of the information items in Appendix A within five to ten business days as outlined in Appendix A.

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- a) The IRB will review your report to determine if any of the information items meet the definitions of serious noncompliance, continuing noncompliance or an unanticipated problem involving risks to subjects or others (UPIRTSO), as listed in “[SOP: DEFINITIONS \(HRP-001\)](#).”
- b) Examples of UPIRTSOs include:
  - i) Internal adverse events that are unexpected, involve new or increased risks, and are related to the research.
  - ii) Changes made to the research without prior IRB approval in order to eliminate apparent immediate harm.
  - iii) Other unanticipated information that is related to the research and participants or others might be at increased risk of harm.
- 13) Submit an updated disclosure of financial interests within thirty days of discovering or acquiring (e.g., through purchase, marriage, or inheritance) a new financial interest.
- 14) Do not accept or provide payments to professionals in exchange for referrals of potential subjects (“finder’s fees.”)
- 15) Do not accept payments designed to accelerate recruitment that are tied to the rate or timing of enrollment (“bonus payments.”)
- 16) See additional requirements of various federal agencies in Appendix B. These represent additional requirements and do not override the baseline requirements of this section.

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

Review the IRB Administration's "[SOP: WRITTEN DOCUMENTATION OF CONSENT \(HRP-091\)](#)". Use the signature block approved by the IRB. Complete all items in the signature block, including dates and applicable checklists.

The following are the requirements for long form consent documents:

- The subject or representative signs and dates the consent document.
- The individual obtaining consent signs and dates the consent document.
- Whenever required by the IRB or sponsor, the subject’s or representative’s signature is to be witnessed by an impartial individual who signs and dates the consent document.
- Whenever the IRB or the sponsor require an impartial witness to the oral presentation, the witness signs and dates the consent document.
- A copy of the signed and dated consent document is to be provided to the subject.
- If the subject is a patient of the UC Davis Health System, a copy of the signed and dated consent form must be placed in the subject’s medical record.

The following are the requirements for short form consent documents (refer to "[WORKSHEET: SHORT FORM OF CONSENT DOCUMENTATION \(HRP-317\)](#)" for additional information on compliant use of the short form method of consent documentation):

- The subject or representative signs and dates the short form consent document and the summary.
- The individual obtaining consent signs and dates the short form consent document and the summary.

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- The impartial witness to the oral presentation signs and dates the short form consent document and the summary.
- Copies of the signed and dated consent document and summary are provided to the subject or representative.
- If the subject is a patient of the UC Davis Health System, a copy of the signed and dated consent form must be placed in the subject’s medical record.

**How do I submit a modification?**

Complete the “[FORM: MODIFICATION \(HRP-213\)](#),” and attach all requested supplements. The PI may sign the submission [electronically](#) by using "Sign this Package" in IRBNet and typing their name and "Signed electronically" on HRP-213 OR sign HRP-213 in ink, scan, and upload the document to IRBNet. The documents must be submitted through IRBNet.

Please note that PIs must not implement the modifications until the IRB approves the modification submission, *unless the modification is intended to protect human subjects from imminent harm.*

Updates to the list of study personnel should be submitted annually or with the continuing review report.

Modifications are categorized into minor changes and significant changes. A ‘minor’ modification is a proposed change in research-related activities that does not significantly affect an assessment of the risks and benefits of the study and does not substantially change the specific aims or design of the study. Minor modifications may be reviewed using the expedited IRB procedure ([WORKSHEET: ELIGIBILITY FOR REVIEW USING THE EXPEDITED PROCEDURE \[HRP-313\]](#)).

A ‘significant’ modification is a proposed change in research-related activities that significantly affects an assessment of the risks and benefits of the study or substantially changes the specific aims or design of the study. Significant modifications require review by the full IRB Committee ([WORKSHEET: CRITERIA FOR APPROVAL AND ADDITIONAL CONSIDERATIONS \[HRP-314\]](#)).

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

Complete the “[FORM: CONTINUING REVIEW PROGRESS REPORT \(HRP-212\)](#),” and attach all requested supplements and submit the documents through IRBNet. The PI may sign the submission [electronically](#) by using "Sign this Package" in IRBNet and typing their name and "Signed electronically" on HRP-212 OR sign HRP-212 in ink, scan, and upload the document to IRBNet.

Before submitting the research for continuing review, you must:

- Determine whether any member of the research staff has a financial interest related to the research. If “yes”, the determination from Conflict of Interest Committee must be submitted to the IRB Administration prior to IRB approval.



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- Ensure that each member of the research team has completed the required [Human Subjects Protection Training](#) and has been trained on the protocol procedures s/he will complete.
- Obtain the verbal or written agreement of each member of the research staff to his/her role in the research.

If the continuing review involves modifications to previously approved research, submit those modifications using the [FORM: MODIFICATION \(HRP-213\)](#) with the continuing review submission. If changes to study personnel have occurred since the last continuing review report was submitted, update the electronic [INITIAL REVIEW APPLICATION](#) with these changes or, if the INITIAL REVIEW APPLICATION was not used in your original submission, submit a revised [FORM HRP-215 RESEARCH PERSONNEL LIST TEMPLATE](#) with the continuing review report.

If the continuing review application is not received by the *administrative due date* in the approval letter, you will be required to develop and implement a suitable corrective and preventive action plan (CAPA).

If the continuing review application is not received by the *protocol expiration date* found in the approval letter, you will be required to develop and implement a suitable CAPA *and* will be restricted from submitting new Human Research until the completed continuing review application has been received and approved.

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 or analysis of private identifiable information. Continuing Human Research procedures during a lapse is a violation of the Institution's policy and, in some cases, 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 research procedures that are not available outside the human research context, submit a "[FORM: Reportable New Information \(HRP-214\)](#)," describing in writing the potential harm enrolled subjects may incur if study procedures are stopped, the procedures that must continue to prevent harm and the number of subjects who need to continue participating in the procedures.

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

Complete the "[FORM: CONTINUING REVIEW PROGRESS REPORT \(HRP-212\)](#)," and attach all requested supplements. The PI may sign the submission [electronically](#) by using "Sign this Package" in IRBNet and typing their name and "Signed electronically" on HRP-212 OR sign HRP-212 in ink, scan, and upload the document to IRBNet. Submit to the IRB Administration via IRBNet. Maintain electronic copies of all information submitted to the IRB in case revisions are required..

If the continuing review application for closing out a Human Research study is not received by the *protocol expiration date* in the approval letter, you will be required to develop and implement

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a suitable CAPA *and* will be restricted from submitting new Human Research until the completed continuing review application has been received and approved.

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

Research records are confidential records and they are university property. Records must be stored safely in your university office or your department or another approved location at the university. Records to be kept include signed IRB records (stored in IRBNet), consent forms, HIPAA authorization forms, case-report forms, tapes or transcripts, and all other data-collection instruments and source documents. If multiple retention requirements apply to the research, the longer requirements will apply. All records must be accessible for inspection and copying by authorized representatives of the IRB, regulatory agencies, and sponsor.

- UCOP requires that signed consent documents are kept for 10 years;
- HHS regulations require records from federally funded research must be kept for 3 years after completion of all research activities;
- FDA regulated research records must be kept for 2 years after a marketing application is approved;
  - For drugs where no application is filed or the application is not approved, the retention period is 2 years after the investigation is discontinued and FDA is notified.
  - Contractual obligations may require records to be maintained per the agreement with the trial sponsor.
- HIPAA requires records involving the generation, disclosure, and/or use of Protected Health Information (PHI) to be retained for at least 6 years after the last subject has completed study activity;

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

Contact the IRB Administration or IRB chair immediately to discuss the situation. If there is no time to make this contact, see the “[WORKSHEET: EMERGENCY USE \(HRP-322\)](#)” for the regulatory criteria allowing such a use and make sure these are followed.

Use the “[TEMPLATE EMERGENCY USE CONSENT DOCUMENT \(HRP-506\)](#)” to prepare your consent document if there is sufficient time to obtain informed consent from the patient or the patient’s legally authorized representative. If there is insufficient time to obtain informed consent, you must consult with a physician who is not a member of the research team to certify, in writing, that the following are true:

- The subject is confronted by a life-threatening situation necessitating the use of the test article.

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- Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
- Time is not sufficient to obtain consent from the subject's legal representative.
- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

You will need to submit a report of the use to the IRB and the certification described above, if applicable, within 5 business days of the use. You must also submit a new project for initial review with a protocol and IRB application within 25 business days.

If you believe you will never need to use the test article in an emergency use situation, contact the IRB Director to be excused from the requirement for protocol submission. If you fail to submit the report within 5 business days or the IRB application for initial review within 25 business days (and do not contact the IRB Director), you will be restricted from submitting new Human Research until the post emergency use requirements are met.

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

Individuals getting an unapproved drug, biologic, or device without prior IRB review cannot be considered a “subject” as defined by DHHS and their results cannot be included in prospective “research” as the term is defined by DHHS.

You should also review and follow the UC Davis Health system policies, Emergency or “Compassionate” Use of Unapproved Drugs, Biologics or Devices (1509) and “Innovative Use Policy (2516)”

### ***What other internal reviews are also involved in the protection of human subject research?***

**Institutional Biosafety Committee (IBC)** – The IBC reviews research involving:

- Recombinant DNA
- Materials that are infectious (or potentially infectious) to plants, animals, or humans (including replication-defective viral vectors)
- Material that falls under the [Cal OSHA Bloodborne Pathogen Standard](#). This includes any work with human cell lines, human blood or blood products, and human body fluids.
- Storage of biohazardous materials that are not being used.

The IBC reviews this research for compliance and conformance with NIH Guidelines, recommends the level of medical surveillance of personnel associated with the research project after review by Occupational Health, and recommends modifications, curtailment, or termination of any projects when it is in the best interest of the health and safety of the

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campus community. If the IRB identifies studies involving recombinant DNA that are not approved by the IBC, the IRB review process will be postponed pending review and approval by the IBC. Investigators may also contact the IBC directly for review requirements.

**Conflict of Interest Committee (COIC)** – Any actual or perceived conflict of interest as defined by institutional policy, consistent with applicable federal and state regulations is required to be reported to and reviewed by the [Conflict of Interest Committee \(COIC\)](#). The COIC will inform the IRB when investigators conducting human research have significant financial interests that constitute a financial conflict of interest. The IRB has the final authority and may grant final approval of research studies with a disclosed conflict of interest, provided that the Principal Investigator has taken appropriate steps to eliminate or manage the conflict, consistent with the Conflict of Interest Committee determination (see [SOP: FINANCIAL CONFLICTS OF INTEREST \[HRP-055\]](#)). Should the IRB or the Conflict of Interest Committee require changes in the research study to mitigate a conflict; the Principal Investigator will be required to submit the revised documents for IRB review and approval.

**Cancer Center Scientific Review Committee (CCSRC)** – The CCSRC is charged with the review and monitoring of protocols involving cancer patients and/or their data or specimens. The Committee provides a centralized mechanism for prospective evaluation of scientific merit, resource allocation, and clinical cancer research monitoring. Principal Investigators must contact the CCSRC for the review and approval of their research study, prior to submission of the protocol for IRB review and approval. The IRB will not approve a protocol involving cancer patients and/or their data or specimens without the approval/exemption of the CCSRC.

**Radiation Use Committee (RUC)** – The RUC is responsible for the surveillance of all uses of radioactive materials and ionizing radiation (including diagnostic x-rays/fluoroscopy/ DEXA) in research involving human participants. Principal Investigators are required to identify, on the “[INITIAL REVIEW APPLICATION](#),” all proposed radiation use. The application requires that Principal Investigators contact the Radiation Use Committee for the review and approval of their study, prior to IRB review and approval. The RUC may require amendments to the design of the study, restrictions, or specific wording in the informed consent document, to ensure conformance with the University’s Radioactive Material License and state and federal regulations. The IRB will not approve a research study involving radiation without the prior approval/exemption of the Radiation Use Committee.

**Stem Cell Research Oversight Committee (SCROC)** – The SCROC 1) provides oversight of all issues related to derivation and use of human adult and embryonic stem cell lines; 2) reviews and approves the scientific merit of research protocols; 3) reviews compliance of all human adult and embryonic stem cell research with all relevant regulations and guidelines; and 4) facilitates education of investigators involved in human adult and embryonic stem cell research. Principal Investigators are required to identify, on the “[INITIAL REVIEW APPLICATION](#),” all human adult and embryonic stem cell studies. The application requires that Principal Investigators contact the Stem Cell Research Oversight Committee for the review and approval of their research study.

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**UCDMC Pathology** – Studies involving any laboratory testing or clinical laboratory sample retrieval, including tissue specimens, require synchronization with the Department of Pathology and Laboratory Medicine. This synchronization should be done in advance of designing your study to coordinate logistics, expectations on deliverables, and the associated costs. Certain types of laboratory tests, activities, and tissue examination may also require prior approval by the Laboratory Section Medical Director.

**IT Evaluation** – Clinical research that requires implementation or use of new applications, systems or devices that collect and/or transmit Protected Health Information (PHI) or Personally Identifiable Information (PII) requires an IT Evaluation prior to the start of the study. The IT Evaluation includes steps to determine if the new technology is secure and complies with UC policies as well as state and federal regulations. It is recommended that the evaluation precede IRB submission to avoid delays in study startup.

### ***How do I get additional information and answers to questions?***

This document and the policies and procedures for the Human Research Protection Program are available on the [IRB Website](#).

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

2921 Stockton Blvd  
Suite 1400, Room 1429  
Sacramento, CA 95817  
Email: [hs-irbeducation@ucdavis.edu](mailto:hs-irbeducation@ucdavis.edu)  
Phone: (916) 703-9151  
Fax: (916) 703-9160

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

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## **Appendix A Prompt Reporting Requirements**

**Report the following information items to the IRB within 5 business days**

***If information contained within a report has previously been submitted to the IRB Administration, do not submit a second time unless the updated report includes new information that would affect or revise the IRB's previous determination. Information that does not fall under any of the categories does not require reporting to the IRB.***

- 1) Information that indicates a new or increased risk, or a new safety issue, for example:
  - a) *New information (e.g., an interim analysis, safety monitoring report, publication, sponsor report, or investigator finding) indicating an increase in the frequency or magnitude of a previously known risk, or reveals a new risk.*
  - b) *Protocol violation that harmed subjects or others or that indicates subjects or others might be at increased risk.*
  - c) *Subject complaint that indicates subjects or others might be at increased risk of harm or at risk of a new harm.*
  - d) *An investigator brochure, package insert, or device labeling is revised to indicate an increase in the frequency or magnitude of a previously known risk, or describe a new risk.*
  - e) *Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a protocol.*
  - f) *Changes significantly affecting the conduct of the clinical trial or increasing the risk to participants.*
- 2) **Serious** harm experienced by a subject or other individual, which in the opinion of the investigator is **unexpected** and **probably related** (>50% likely; "Don't know" = <50%) to the research procedures.
  - *A harm is "serious" when it meets any of the following criteria; 1.) results in death; 2.) is life-threatening (places the subject at immediate risk of death from the event as it occurred); 3.) results in inpatient hospitalization or prolongation of existing hospitalization; 4.) results in a persistent or significant disability/incapacity; 5.) results in a congenital anomaly/birth defect; 6.) based upon appropriate medical/psychological judgment, may jeopardize the subject's health and may require medical, counseling, or surgical intervention to prevent one of the other outcomes listed in this definition; or 7.) results in criminal or civil liability or damaging of the subject's financial standing, employability, or reputation.*
  - *A harm is "unexpected" when its specificity or severity are inconsistent with risk information previously reviewed and approved by the IRB in terms of nature, severity, frequency, and characteristics of the study population.*
  - *A harm is "probably related" to the research procedures if in the opinion of the investigator, the research procedures more likely than not caused the harm.*
- 3) Change to the protocol done without prior IRB review to eliminate an apparent immediate hazard to a subject.

**Report the following within 10 business days:**

- 4) Non-compliance with the federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance.
- 5) Failure to follow the protocol due to the action or inaction of the investigator or research staff.
- 6) Breach of confidentiality (inappropriate disclosure of or access to confidential information).
- 7) Complaint of a subject that cannot be resolved by the research team.
- 8) Premature suspension or termination by the sponsor, investigator, or institution.
- 9) Incarceration of a subject in a study not approved by the IRB to involve prisoners.
- 10) Inquiry by a federal agency and any reports (e.g., FDA Form 483).

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- 11) Ancillary approvals (e.g. CoC, SCRO) that do not result in a protocol revision; written reports by study monitors and auditors that include reportable events that have not yet been reported<sup>[1]</sup>; Data Safety Reports that include a recommendation to terminate or modify a study.
- 12) Unanticipated adverse device effect (any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects).
- 13) Other: information or situations that do not meet any of the above criteria.

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<sup>[1]</sup> The IRB requires only audit and monitoring reports that include information that must be reported under any of the other numbered items above. If the report does not include reportable information, you do not need to submit it. If the monitoring report includes information that falls under category 1(b), 4, 5, or 6 please include a preventive action plan, indicate whether the event was previously reported or include a statement that you will submit separate or updated RNIs with preventive action plans for the new reportable events included on the report.

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**Appendix B-1 Additional Requirements for DHHS-Regulated Research<sup>2</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>2</sup> “Guidance on Withdrawal of Subjects from: Data Retention and Other Related Issues”  
<http://www.hhs.gov/ohrp/policy/subjectwithdrawal.html>



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## **Appendix B-2 Additional Requirements for FDA-Regulated Research**

1. The FDA defines a human subject as: An individual who is or becomes a subject in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. When medical device research involves in vitro diagnostics and unidentified tissue specimens the FDA defines the unidentified tissue specimens as human subjects.
2. When a subject withdraws from a study:<sup>3</sup>
  - a. The data (including specimens) 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.
3. For FDA-regulated research involving investigational drugs:
  - a. Investigators must abide by FDA restrictions on promotion of investigational drugs:<sup>4</sup>
    - i. For clinical investigations requiring an Investigational New Drug Exemption (IND), the IRB will not approve the investigation until one of the following are satisfied:
      1. The IRB receives evidence that an IND has been approved (e.g. including of an IND number on the protocol or other sponsor document); or

<sup>3</sup> "Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials"  
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126489.pdf>

<sup>4</sup> "Promotion of investigational drugs"  
<http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.7>

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2. The IRB receives evidence that an IND application was received by the FDA and 30 calendar days have elapsed with no communication(s) from the FDA.
  - ii. 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.
  - iii. 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.
  - iv. An investigator must not commercially distribute or test market an investigational new drug.
- b. Follow FDA requirements for general responsibilities of investigators<sup>5</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.
  - 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>6</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>7</sup>
  - i. Disposition of drug:
    1. An investigator is required to maintain adequate records of the receipt, storage, and disposition of the drug, including dates, quantity, and use by subjects.

<sup>5</sup> “General responsibilities of investigators”

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

<sup>6</sup> “Control of the investigational drug”

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

<sup>7</sup> “Investigator recordkeeping and record retention”

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

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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>8</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:
    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>9</sup>

<sup>8</sup> "Investigator reports" <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=312.64>

<sup>9</sup> "Assurance of IRB review" <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=312.66>

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- 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>10</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>11</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.
    - ii. Follow California requirements for controlled substances for research taking place in California.<sup>12</sup> Contact legal counsel for requirements of other states and countries.
    - iii. Follow University of California requirements for controlled substances.<sup>13</sup>
  - i. For investigator-initiated research involving investigational drugs, follow FDA requirements in 21 CFR Part 312, Subpart B for obtaining Investigational New Drug (IND) clearance/approval.
    - i. Follow "WORKSHEET: DRUGS (HRP-306)" for information concerning legal and regulatory requirements that apply to the use of investigational test articles.
4. For FDA-regulated research involving investigational devices:

<sup>10</sup> "Inspection of investigator's records and reports"

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

<sup>11</sup> "Handling of controlled substances"

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

<sup>12</sup> "State of California Research Advisory Panel Guidelines" <http://oag.ca.gov/research/guide>

<sup>13</sup> "University of California Business and Finance Bulletin: Controlled Substances Program"

<http://www.ucop.edu/ucophome/policies/bfb/bus50.pdf>

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- a. General responsibilities of investigators.<sup>14</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>15</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.
    1. When the IRB determines an Investigational Device Exemption (IDE) is required for a clinical investigation, the IRB will not approve the investigation until one of the following are satisfied:
      - a. The IRB receives a copy of a letter from the FDA indicating that an IDE has been approved; or
      - b. The IRB receives evidence that an IDE application was received by the FDA and 30 days have elapsed with no communication(s) from the FDA.
  - 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.

<sup>14</sup> "Investigational Device Exemptions General responsibilities of investigators"  
<http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=812.100>

<sup>15</sup> "Investigational Device Exemptions Specific responsibilities of investigators"  
<http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=812.110>

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- 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>16</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.
  - 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.

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<sup>16</sup> "Investigational Device Exemptions Records"  
<http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.140>

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- d. Inspections<sup>17</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>18</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.

<sup>17</sup> "Investigational Device Exemptions Inspections"

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

<sup>18</sup> "Investigational Device Exemptions Records and Reports"

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

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- 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.
- f. For investigator-initiated research involving investigational devices, follow FDA requirements in 21 CFR Part 812, Subpart B for obtaining Investigational Device Exemption (IDE) approval.
- i. Follow “WORKSHEET: DEVICES (HRP-307)” for information concerning legal and regulatory requirements that apply to the use of investigational test articles.



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**Appendix B-3 Additional Requirements for Clinical Trials (ICH-GCP)<sup>19</sup>**

1. The protocol includes sufficient information about the test article to support conducting the clinical trial
2. 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 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.
3. 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.
4. 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 should ensure that adequate medical care is provided to a subject for any adverse events,

<sup>19</sup> [Guidance for the Industry, E6 Good Clinical Practice](#)

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including clinically significant laboratory values, related to the trial. The investigator 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.
5. Communication with IRB
- a. Before initiating a trial, the investigator 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 written application to the IRB, the investigator 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 should supply a copy of the updated Investigator's Brochure to the IRB.
  - c. During the trial the investigator should provide to the IRB all documents subject to review.
6. Compliance with Protocol
- a. The investigator 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 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.
7. Investigational Product
- a. The sponsor or sponsor-investigator should include a description of the manufacturing, handling, and storage in accordance with applicable good manufacturing practice (GMP).
  - b. Responsibility for investigational product accountability at the trial site rests with the investigator.

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- c. Where required, the investigator should assign some or all of the investigator'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.
  - d. The investigator and/or a pharmacist or other appropriate individual, who is designated by the investigator, 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.
  - e. The investigational product should be stored as specified by the sponsor and in accordance with applicable regulatory requirements.
  - f. The investigator should ensure that the investigational product are used only in accordance with the approved protocol.
  - g. The investigator, or a person designated by the investigator, 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.
  - h. 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.
8. Informed Consent of Trial Subjects
- a. If the research subject of a study funded by the DoD or its components meets the definition of "experimental subject"<sup>20</sup> then a waiver of consent [including an exception from informed consent in emergency medicine research] by the IRB is prohibited unless a waiver is obtained from the Assistant Director of Defense for Research and Engineering. However, if the research subject does not meet the definition of an "experimental subject," then the IRB may waive the consent process.
  - b. 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.

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<sup>20</sup> Research Involving a human being as an "experimental subject" includes an activity, for research purposes, where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction. This definition does not include activities that are not considered research involving human subjects, activities that meet the exemption criteria and research involving the collection or study of existing data, documents, records, or specimens from living individuals.

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- c. The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB's approval opinion in advance of use. The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.
- d. Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.
- e. None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally authorized representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.
- f. The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally authorized representative, of all pertinent aspects of the trial including the written information and the approval opinion by the IRB.
- g. The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally authorized representative and the impartial witness, where applicable.
- h. Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally authorized representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally authorized representative.
- i. Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally authorized representative, and by the person who conducted the informed consent discussion.
- j. If a subject is unable to read or if a legally authorized representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally authorized representative, and after the subject or the subject's legally authorized representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally authorized

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representative, and that informed consent was freely given by the subject or the subject's legally authorized representative.

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

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- 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.
- l. Prior to participation in the trial, the subject or the subject's legally authorized representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally authorized representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.
- m. When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally authorized representative (e.g., children, or incompetent patients), 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.
- n. 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 informed consent form.
- o. Non-therapeutic trials may be conducted in subjects with consent of a legally authorized representative provided the following conditions are fulfilled: a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally. b) The foreseeable risks to the subjects are low. c) The negative impact on the subject's well-being is minimized and low. d) The trial is not prohibited by law. 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. (See "CHECKLIST: COGNITIVELY IMPAIRED ADULTS (HRP-417)" for full requirements related to adults who lack capacity to provide legally effective consent.)
- p. In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally authorized representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally authorized representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval opinion by the IRB, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally authorized representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested. (See "WORKSHEET: EMERGENCY USE (HRP-322)" and "CHECKLIST: WAIVER OF CONSENT PROCESS FOR

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EMERGENCY RESEARCH (HRP-419)” for full requirements related to emergency use.)

9. 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 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 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 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.
- g. Upon request of the monitor, auditor, IRB, or regulatory authority, the investigator should make available for direct access all requested trial-related records.

10. 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.

11. 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

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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 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 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 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 should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.
12. Final Reports by Investigator: Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator 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 B-4 Additional Requirements for Department of Defense (DOD) research**

1. When appropriate, research protocols must be reviewed and approved by the IRB prior to the Department of Defense approval. Consult with the Department of Defense funding component to see whether this is a requirement.
2. Employees of the Department of Defense (including temporary, part-time, and intermittent appointments) may not be able to legally accept payments to participate in research and should check with their supervisor before accepting such payments. Employees of the Department of Defense cannot be paid for conducting research while on active duty.
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. Civilian researchers attempting to access military volunteers should seek collaboration with a military researcher familiar with service specific requirements.
5. Components of the Department of Defense might have stricter requirements for research-related injury than the DHHS regulations.
6. The training requirements listed in the [‘What training do my staff and I need to conduct Human Research?’](#) section of this Manual apply to all personnel who conduct, review, approve, oversee, support, or manage human subjects research. Depending on the project, there may be additional, specific educational requirements or certification required. Any additional requirements will be directed by the funding agency, Sponsored Programs, Legal Affairs, Compliance, Contracts, your department, and/or the IRB Administration.
7. 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.
8. When research involves U.S. military personnel, policies and procedures require limitations on dual compensation:
  - a. Prohibit an individual from receiving pay of 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.
9. When conducting multi-site research, a formal agreement between Institutions is required to specify the roles and responsibilities of each party.
10. Investigators must submit research approval documents to the DoD Component for administrative review of the research before the research can begin. The research cannot start until the DoD component provides confirmation that the study may begin.

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11. The following shall be promptly reported to the DOD human research protection officer:
  - a. When significant changes to the research protocol are approved by the IRB.
  - b. The results of IRB continuing review
  - c. Change of reviewing IRB;
  - d. When the institution or investigator is notified by any Federal Department, agency or national organization that any part of the HRPP is under investigation for cause involving a DOD supported research protocol.
  
12. Other specific requirements of Department of Defense Research can be found in the “Additional Criteria for Department of Defense (DOD) Research” section in the IRB’s “WORKSHEET: ADDITIONAL FEDERAL CRITERIA (HRP-318),” and in “SOP: NEW INFORMATION (HRP-024).”

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

1. You must report the following within ten business days to the Department of Energy human subject research program manager:
  - a. Any significant adverse events, unanticipated risks; and complaints about the research, with a description of any corrective actions taken or to be taken.
  - b. Any suspension or termination of IRB approval of research.
  - c. Any significant non-compliance with HRPP procedures or other requirements.
2. You must report the following within three business days to the Department of Energy human subject research program manager:
  - a. Any compromise of personally identifiable information must be reported immediately.<sup>21</sup>
3. Other specific requirements of Department of Energy (DOE) Research can be found in the “Additional Requirements for Department of Energy (DOE) Research” section in the IRB’s “WORKSHEET: ADDITIONAL FEDERAL CRITERIA (HRP-318).”

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<sup>21</sup> Upon Discovery

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**Appendix B-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. The project must have adequate research design and contribute to knowledge about corrections.
5. Investigators must observe the rules of the institution or office in which the research is conducted.
6. 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.
7. The research must be reviewed and approved by the Bureau Research Review Board.
8. 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 AND participating in authorized research being conducted by Bureau employees or contractors.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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, an investigator may not guarantee confidentiality when the subject indicates intent to commit future criminal conduct or harm himself or herself or someone else, or, if the subject is an inmate, indicates intent to leave the facility without authorization.
  - e. A statement that participation in the research project will have no effect on the inmate subject's release date or parole eligibility.
14. You must have academic preparation or experience in the area of study of the proposed research.
15. 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.
16. The IRB application must include a comprehensive statement, which includes:
- a. Review of related literature.
  - b. Detailed description of the research method.
  - c. Significance of anticipated results and their contribution to the advancement of knowledge.
  - d. Specific resources required from the Bureau of Prisons.
  - e. Description of all possible risks, discomforts, and benefits to individual subjects or a class of subjects, and a discussion of the likelihood that the risks and discomforts will actually occur.
  - f. Description of steps taken to minimize any risks.
  - g. Description of physical or administrative procedures to be followed to ensure the security of any individually identifiable data that are being collected for the study.
  - h. Destroy research records or remove individual identifiers from those records when the research has been completed.
  - i. Description of any anticipated effects of the research study on Institutional programs and operations.
  - j. Relevant research materials such as vitae, endorsements, sample consent statements, questionnaires, and interview schedules.

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17. The IRB application must include a statement regarding assurances and certification required by federal regulations, if applicable.
18. You must assume responsibility for actions of any person engaged to participate in the research project as an associate, assistant, or subcontractor.
19. At least once a year, you must provide the Chief, Office of Research and Evaluation, with a report on the progress of the research.
20. 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.
21. You must include an abstract in the report of findings.
22. In any publication of results, you must acknowledge the Bureau's participation in the research project.
23. You must expressly disclaim approval or endorsement of the published material as an expression of the policies or views of the Bureau.
24. 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.
25. Other specific requirements of 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 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 B-7 Additional Requirements for Department of Education (ED) Research**

1. Each school at which the research is conducted must provide an assurance that they comply with the Family Educational Rights and Privacy Act (FERPA) and the Protection of Pupil Rights Amendment (PPRA).
2. Provide a copy of all surveys and instructional material used in the research. Upon request, parents of children<sup>22</sup> involved in the research<sup>23</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 Requirements for Department of Education (ED) Research” section in the IRB’s “WORKSHEET: ADDITIONAL FEDERAL CRITERIA (HRP-318).”

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<sup>22</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>23</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.

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

1. Research conducted, supported, or intended to be submitted to EPA is subject to Environmental Protection Agency Regulations.
2. Intentional exposure of pregnant women or children to any substance is prohibited.
3. Observational research involving pregnant women and fetuses are subject to 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.
5. Other specific requirements of 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).”