



DIVISION OF RESEARCH
Institutional Review Boards

Investigator Manual

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Scope

Throughout this document, "organization" refers to The University of Houston.

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 organization.

General information regarding Human Research protections and relevant federal regulations and guidance is incorporated into the required human protections training. For additional information see below: "What training do my research team and I need to conduct Human Research?"

What is Research?

RESEARCH is defined as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge¹." Student theses and dissertations, by default, are designed to contribute to generalizable knowledge. Individual projects in research methods courses may or may not fall under the definition of "Research," based on the ultimate intent of disseminating results, however such activity does require notification to the IRB office if the project involves typical research-related activities (including but not limited to informed consent, interviews, focus groups, and surveys involving human subjects).

What is Human Research?

HUMAN SUBJECT means a living individual about whom an investigator (whether professional or student) conducting research (i) obtains information or biospecimens through intervention or interaction with the individual, and uses studies, or analyzes the information or biospecimens; or (ii) obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. ²

An algorithm for determining whether an activity is Human Research can be found in the "WORKSHEET: Human Research Determination (HRP-310)," located under the "Worksheets" tab in the ICON library. Use this document for guidance as to whether an activity meets either the DHHS or FDA definition of Human Research, keeping in mind that the IRB makes the ultimate determination in questionable cases as to whether an activity constitutes Human Research subject to IRB oversight.

You are responsible for not conducting Human Research without prior IRB review and approval (or an organizational review and approval of exempt Human Research). If you

¹ 45 CFR 46.103(d)

² 45 CFR 46.102(f)

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have questions about whether an activity is Human Research, contact the IRB Office any time at CPHS@central.uh.edu, and they will provide you with a determination.

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

All study team members, including faculty sponsors for student research, must complete the Collaborative Institutional Training Initiative (CITI) human subjects online training program. In the case of research team members who are not directly associated with UH, the National Institutes of Health (NIH) Protection Human Research Participants Course (PHRP) will be accepted. Other institutions' training requirements may be considered for acceptance. You may have additional training imposed by other federal, state, or organizational policies. Please visit www.citiprogram.org to complete one of the following modules:

- Group 1: Biomedical and Physical Science Research Investigators and Graduate Students,
OR
- Group 2: Social and Behavioral Research Investigators and Graduate Students,
or
- If conducting research that collects or uses Protected Health Information (PHI), the Information Privacy & Security Training must also be taken.
- If collecting educational data, the Family Educational Rights and Privacy Act (FERPA) training is also required.

Human subjects training completion is pulled into the ICON online system from CITI. If the training does not populate into the "training" tab in ICON, the team member should log into his/her CITI account to verify that their profile matches the ICON account profile exactly (name and @UH email address). Accounts linked to email addresses other than .UH.edu will not link to the online system. If the name and email address do not match, the CITI profile should be updated to reflect the correct information as it appears in ICON. Training must be completed for all team members listed on the IRB protocol (including faculty sponsors for student research) before IRB approval is granted.

If CITI training was completed at another institution, log into the existing CITI account and choose "Affiliate with Another Institution." Add the University of Houston and complete the registration process. Note that there may be additional modules to complete to fulfill the UH training requirements.

Training is valid for a three-year period, after which time a refresher course must be taken. All study team members should be provided with a copy of the approved protocol and be trained specifically to approved protocol requirements and processes.

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

Individuals involved in research, research consultation, teaching, professional practice, institutional committee memberships, and service on panels such as the Institutional Review Board or Data and Safety Monitoring Boards are considered to have an institutional responsibility³.

All individuals responsible for the design, conduct, or reporting of research are required to disclose their financial interests that are related to the research listed in the "Financial Interest Declaration" sections of the Initial Study ("Basic Information," Q6) and Continuing Review (Continuing Review Q3) SmartForms:

- On submission of an initial review.
- At least annually as part of continuing review.
- Within 30 days of discovering or acquiring (e.g., through purchase, marriage, or inheritance) a new financial interest.

To disclose an outside financial interest, answer the IRB SmartForm question as "yes." This will create a certification in the ICON research Conflict of Interest (COI) module that will require your submission. Depending on the potential for bias related to the financial interest that may be perceived, the Conflict of Interest Committee may require a management plan to manage one or more of the disclosed financial interests. Each management plan is unique to the specific research and related conflict and could include, for example, the requirement to disclose the interest in publications, presentations, and/or the consent form, limiting a study team member's engagement, blinding, and/or data monitoring.

Additional information on submitting conflict of interest certifications and disclosures and related training can be found on the research [COI policy website](#) or by contacting COI@central.uh.edu.

How do I submit new Human Research to the IRB?

Click "Create New Study" to open the electronic SmartForm in the IRB module of the ICON system and attach all supplemental documentation applicable to the proposed study (protocol, consent forms, letters of cooperation, study instruments, etc.). It is important to note that the protocol should be fully developed on the HRP-503 template, located under the "Templates" tab of the IRB Library in ICON, before beginning the

³ From the [UH Conflict of Interest in Research Policy](#), investigator definition: An investigator is defined as the project director or principal investigator, and any other persons, regardless of title or position, who are responsible for the design, conduct, or reporting of research or educational activities funded or proposed for funding.

Therefore, this policy can apply to collaborators, consultants, post-doctoral fellows, graduate students, and others who meet the threshold for responsibility. At a minimum, all individuals listed as an investigator or key personnel on a research project must file a certification. It is the responsibility of the PI to determine if other research team members meet this threshold based on their role in the research.

A research COI certification is also required if a researcher has a financial interest that may reasonably appear to be related to his/her engagement in human or animal subjects research, regardless of funding.

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submission process as the SmartForm will not advance past the first page until the protocol document is attached. Consent and assent form templates are also located under this tab.

Before submitting a research protocol to the IRB, applicable ancillary reviewers must be assigned. The key role of the ancillary review is to attest that they have examined the proposal and find that the information is complete and that the scientific or scholarly validity of the project has been assessed and found to be appropriate. They certify that the resources necessary to protect human participants are available. They assume the responsibility for ensuring: the competence, integrity, and ethical conduct of the investigator(s); that no procedural changes relating to the human subjects involved will be allowed without prior review by the Human Subjects Protection Program; they are satisfied that the procedures to be used for obtaining informed consent comply with the spirit and intent of DHHS and FDA regulations, and that the investigator(s) is/are fully competent to accomplish the goals and techniques stated in the proposal.

In addition, if one Departmental/College reviewer is on leave, the other may submit the review; this should be worked out between these parties. Assigned reviewers are as follows:

- For faculty protocols, both a Chair and a Dean level ancillary reviewer must be assigned. Please review the "Designated Ancillary Reviewers" document in the ICON Library under the "General" tab. Only ONE of these reviews must be completed prior to submitting to the IRB, however both must be assigned. In some cases, the college or department has assigned a third reviewer to attend to the day-to-day reviews, however the Chair and Dean will still receive notification that the protocol has been submitted.
- For student-led protocols, in addition to the Chair/Dean ancillary reviewers, the faculty sponsor must also be added as an ancillary reviewer and must complete a review prior to submission.
- Biosafety must be added as an ancillary review if the project intends to collect or use human biological specimens (saliva, blood or urine) or recombinant agents, as additional review and training are required by Environmental Health and Life Safety (EHLS).
- Your college may require other ancillary reviewers. Please check with the applicable Associate Dean for Research.

Once ancillary reviews have been obtained, the PI or PI proxy may submit the SmartForm by clicking the "Submit" activity. Before submitting the research for initial review, you must:

- Obtain the financial interest status ("yes" or "no") of each research team member.
- Obtain the agreement of each research staff to his/her role in the research.

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It should be noted that while the PI Proxy may submit protocols and updates on behalf of the PI, the PI is ultimately responsible for the conduct of the research and compliance with federal, state, funding agency, and institutional requirements related to the protection of human subjects.

How do I write an Investigator Protocol?

Use the “TEMPLATE PROTOCOL (HRP-503),” found in the ICON library as a starting point for drafting a new Investigator Protocol. Here are some key points to remember when developing the protocol:

- The italicized bullet points in the “TEMPLATE PROTOCOL (HRP-503)” serve as guidance to investigators when developing an Investigator Protocol for submission to the IRB. These are items the IRB must consider when reviewing research, and the protocol review may be delayed if these points are not addressed.
- When writing an Investigator Protocol, always keep an electronic copy. This document may require modification when responding to the IRB’s feedback and making future changes to the Investigator Protocol. It is helpful to number the versions as you make changes.
- Depending on the nature of the research, certain sections of the template may not apply to the research design. Please see the HRP 503 Protocol template for detailed instructions on how to complete the form.
- Individuals who are members of the following vulnerable populations may not be specifically targeted for recruitment as research subjects unless expressly stated within the inclusion criteria:
 - Adults unable to provide legally effective consent
 - Individuals who are not yet adults (infants, children, teenagers)
 - Pregnant women
 - Prisoners
 - Economically or educationally disadvantaged persons

While these groups may be considered for inclusion in research, the IRB is required to review for additional regulatory criteria/protections. Ensure that all questions related to vulnerable populations are addressed within the protocol template. The IRB office is available for guidance regarding these additional criteria/protections. Checklists utilized by the IRB to review such research are also available to you in the ICON Library.

- If UH students will be recruited as research participants, this must be identified in the protocol. In most cases, an individual with access to or influence on the

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student's grades may not be involved in recruitment or informed consent, or in the review of identifiable data for the study. This addresses the IRB requirement to avoid undue influence in subject selection. If extra credit will be offered as an incentive for participation, it may not be the only method by which extra credit may be earned in the course.

How do I create a consent document?

Use the applicable "TEMPLATE CONSENT DOCUMENT (HRP-502a-e)" located in the ICON Library to create consent and parental permission documents, and the "TEMPLATE CHILD ASSENT" to formulate assent documents and scripts. Written parental permission and child assent are required for most research involving subjects under the age of eighteen.

Note that all consent documents must contain the required elements of informed consent as well as all additional appropriate elements defined by federal regulations. The templates provided contain these elements. ***Please ensure documents are professional in nature by maintaining consistent fonts and sizes throughout the document and by reviewing for spelling and grammar mistakes. Consent documents should be at no higher than an 8th grade reading level (spell out or simplify difficult terms and professional jargon).***

Review the "Long Form of Consent Documentation" section in the IRB's "WORKSHEET: Criteria for Approval (HRP-314)" to ensure that these elements are addressed. When using short form consent documentation, the appropriate signature block from "Template Consent Document (HRP-502)" should be used on the short form.

Some studies may qualify for a waiver of documented consent (for example, low-risk survey research in which identifying information is not collected). In these cases, all elements of informed consent must still be provided, although physical signature is waived. In other cases (such as review of archival data), the consent process may be waived altogether. Both of these options require that specific regulatory criteria are met; please review "CHECKLIST: Waiver or Alteration of the Consent Process (HRP-410)" and "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" if you believe one of these options may apply, and provide the requested justifications in the protocol.

Once approved, consent documents will be watermarked with an approval and expiration date. ***Please utilize only the watermarked version to obtain subject consent.*** This ensures that only the current IRB-approved version is used and helps to avoid noncompliance.

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

Submitted activities will fall under one of the following five regulatory classifications:

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- **Not Research:** Activities must meet the definition of “Research” to fall under IRB oversight. If a project does not meet the definition of research provided above (for example, it is not intended to generate generalizable information), a submission to the IRB is not required. Contact the IRB Office in cases where it is unclear whether an activity is Human Research. All theses and dissertations meet the “generalizable information” threshold.
- **Not Human Subjects:** Activities must involve “Human Subjects” to fall under IRB oversight. Activities that do not meet the definition above are not subject to IRB oversight or review. Review the “WORKSHEET: Human Research (HRP-310),” located under the “Worksheets” tab of the ICON library for reference. Contact the IRB Office in cases where it is unclear whether an activity is Human Subjects Research.
- **Exempt Review:** Certain categories of Human Research may be exempt from regulation but still require IRB office/institutional review. Some specific categories may require limited IRB review (review by the IRB Chairperson or one or more experienced members). It is the responsibility of the institution, not the investigator, to determine whether Human Research is exempt from IRB review; therefore, a protocol must be submitted in ICON. Review the “WORKSHEET: Exemption Determination (HRP-312),” located under the “Worksheets” tab of the ICON library for reference on the categories of research that may be exempt.
- **Expedited Review:** Certain categories of non-exempt Human Research defined by the regulations may qualify for review using an expedited procedure. This means that the project may be reviewed by a single designated IRB member, rather than a fully convened board. Review the “WORKSHEET: Expedited Review (HRP-313),” located under the “Worksheets” tab of the ICON library, 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 expedited review must be reviewed by the convened IRB. The fully convened IRB meets monthly; submission deadlines and meeting dates can be found on the IRB’s website.

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, defer research, or disapprove research.

- **Approve:** This determination is 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:** This determination is made when the IRB or designated reviewer requires specific, clear-cut modifications to the research before approval can be granted. This means that all regulatory review

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criteria as stated in the HRP 314 have been met; however additional modifications or documents must be provided for the protocol to be considered complete (for example, minor modifications to consent forms, revision of a flyer, or completion of training). Modifications may be reviewed by the IRB office staff.

- **Deferred:** This determination is made when the convened IRB determines that regulatory review criteria either have not been met, or that not enough information is provided to determine if these criteria have been met (for example, risks to subjects are unclear or not minimized, subject selection is not equitable, the consent process described is not approvable). When making this motion, the IRB describes its reasons for this decision, offers suggestions for revisions to address these concerns, and provides the investigator an opportunity to respond by providing additional information or justification to the IRB. Responses to a deferred protocol require review by the full committee at a convened IRB meeting.
- **Disapprove:** This determination is made when the IRB determines that it is unable to approve research because the protocol does not meet regulatory approval criteria and the IRB also cannot describe modifications that might make the research approvable in its current state or design. When making this motion, the IRB describes its reasons for this decision and gives the investigator an opportunity to re-write and resubmit the protocol. The investigator may request to be allotted time in a convened meeting to discuss the issues with the board. The research may also be disapproved at an institutional level if it involves subject areas or procedures unacceptable to the university's vision or mission. The Institutional Official may not approve a study if the IRB has disapproved it. Protocols that are disapproved require a full re-design and a new submission to be reconsidered by the IRB/institution.

How does the IRB decide whether to approve Human Research?

Applications are reviewed based upon "WORKSHEET: Criteria for Approval (HRP-314)." The IRB must ensure the following in order to approve research involving human subjects:

(1) Risks to subjects are minimized:

- (i) By using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk, and
- (ii) Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The

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IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted. The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by 45 CFR 46.116.

(5) Informed consent will be appropriately documented or appropriately waived in accordance with 45 CFR 46.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

More detail regarding approval criteria can be found in "WORKSHEET: Criteria for Approval (HRP-314)." This worksheet also contains all applicable elements and considerations for informed consent, and references other checklists that might be relevant. All checklists and worksheets can be found in the ICON library.

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.

What will happen after IRB review?

The IRB will provide the Principal Investigator with a written decision indicating one of the determinations above.

- **If the IRB approves the research:** The research may commence once all other organizational approvals have been met (for example, biosafety approval may be required, applicable conflict of interest disclosures must be up to date). IRB approval for full board protocols is typically granted for one year; the expiration date is noted in the approval letter. Approval of the research expires on the expiration date with no exceptions; a continuing review submission must be made prior to expiration and approved by the IRB or IRB office to continue active approval. Research conducted without active IRB approval is noncompliant with federal regulations and institutional requirements and may have significant consequences. Research approved under exempt and expedited review

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procedures typically has no expiration; however, follow-on submissions such as modifications and reportable information must be submitted for all protocols, regardless of review mechanism, to maintain compliance.

- **If the IRB requires modifications to secure approval:** Make the requested modifications to the protocol and relevant documents and submit them to the IRB office through ICON. Please use track changes to revise any documents. If all requested modifications are made and addressed adequately, the IRB will issue a final approval letter. Research may not commence until this final approval letter is received. If the PI does not agree with the requested modifications, detailed response and appropriate justification should be returned. The IRB will consider this information and respond to the investigator.
- **If the IRB defers the research:** The IRB will provide a statement of the reasons for deferral and suggestions to make the study approvable, and provide an opportunity to respond in writing. Once returned to the IRB, the protocol will need to be re-reviewed by the full committee. Please use track changes to revise any documents. If the IRB's reasons for the deferral are addressed in a resubmission and all approval criteria are met, the research can be approved. Any minor issues remaining may be determined to constitute "modifications needed to secure approval (see above).
- **If the IRB disapproves the research:** The IRB will provide a statement of the reasons for disapproval and give the PI an opportunity to respond in writing. The application must be submitted as a new protocol after substantial changes have been made to the proposed study. The investigator cannot conduct any research activities that have been disapproved by the IRB.

In all cases, you have the right to work directly with the IRB and IRB office to address required corrections and their concerns regarding IRB review.

What are my obligations as a PI after IRB approval?

- 1) Human Research activities, including advertisement and recruitment, may not commence until a final IRB approval letter has been issued in ICON.
- 2) Human Research activities may not begin until all other required institutional approvals have been obtained.
- 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 Team Members remain 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) Personally conduct or supervise Human Research.
 - a) Conduct the Human Research based on the relevant current protocol as approved by the IRB.

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- b) Ensure that consent or permission is obtained according to the relevant current approved protocol.
- c) Do not initiate modifications to research without prior IRB review and approval unless necessary to eliminate apparent immediate hazards to subjects (such changes must be reported to the IRB as soon as possible with adequate justification).
- d) Protect the rights, safety, and welfare of all subjects involved in the research.
- 6) Submit to the IRB:
 - a) Any proposed modifications as described in this manual, including changes to study personnel. (See “How do I submit a modification?”)
 - b) A continuing review application annually or otherwise as requested in the approval letter. (See “How do I submit continuing review?”)
 - c) A continuing review application when the Human Research protocol is to be closed. (See “How Do I Close Out a Study?”)
- 7) Report required information to the IRB within five business days:
 - a) Information that indicates a new or increased risk, or a new safety issue. For example:
 - i) New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor report, or investigator finding) that indicates an increase in the frequency or magnitude of a previously known risk, or uncovers a new risk
 - ii) Protocol violation that harmed subjects or others or that indicates subjects or others might be at increased risk of harm
 - iii) Complaint of a subject that indicates subjects or others might be at increased risk of harm or risk of a new harm
 - iv) Any changes significantly affecting the conduct of the research
 - b) Harm experienced by a subject or other individual, which in the opinion of the investigator are **unexpected** and **probably related** to the research procedures.
 - (1) Harm is “**unexpected**” when its specificity or severity are inconsistent with risk information previously reviewed and approved by the IRB regarding nature, severity, frequency, and characteristics of the study population.
 - (2) 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.
 - c) Noncompliance with the federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such noncompliance. Please note that instances of noncompliance, such as over-enrollment of subjects or conducting research before approval or following the expiration of the protocol (i.e., without IRB approval) may result in corrective action, including not using the noncompliant data for research purposes.
 - d) Audit, inspection, or inquiry by a federal agency and any resulting reports.
 - e) Written reports of study monitors.
 - f) Failure to follow the protocol due to the action or inaction of the investigator or research staff

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- g) Breach of confidentiality, including but not limited to loss or theft of identifiable research data.
 - h) Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject
 - i) Incarceration of a subject in a study not approved by the IRB to involve prisoners, if you wish for that subject to continue participation while incarcerated.
 - j) Complaint from a subject that cannot be resolved by the research team.
 - k) Premature suspension or termination of the protocol by the sponsor, investigator, or institution.
- 8) Ensure all team members submit an updated conflict of interest disclosure within thirty days of discovering or acquiring (e.g., through purchase, marriage, or inheritance) a new financial interest that may be related to the research.
 - 9) Follow additional requirements of federal agencies that fund and/or oversee the research (such as the FDA or Department of Education) detailed in the appendices to this document and in "WORKSHEET: ADDITIONAL FEDERAL AGENCY CRITERIA (HRP-318)". These represent additional requirements and do not override the baseline requirements of this section.
 - 10) Ensure that your study is registered on clinicaltrials.gov if required. FDA-regulated clinical trials, NIH-funded clinical trials (note that the FDA and NIH use different criteria to define what constitutes a clinical trial) and other unfunded studies with an intent to publish in an ICMJE journal require registration in ClinicalTrials.gov. Other federally funded studies are required by the new common rule to post a copy of the consent form on a publicly available federal website that will be established as a repository; registration on Clinicaltrials.gov can fulfill this requirement. See the UH IRB website for more information and helpful tips.

How do I document consent?

Use the signature block approved by the IRB. Complete all items in the signature block, including dates. Please keep in mind that consent is a process and not simply a document; it should represent an ongoing dialogue between the study team and the subject.

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 the IRB or the sponsor requires a witness or for subjects who cannot read and whenever required by the IRB or the sponsor, a witness to the oral presentation signs and dates the consent document. The subject can indicate their consent by "making their mark" on the consent document.
- A copy of the signed and dated consent document is to be provided to the subject. A signed and dated copy must also be maintained in the research

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record, separate from identifiable data. The key to coded data must also be maintained separate from identifiable data and consent forms.

The following are the requirements for Waiver of documentation of Consent:

- This waiver is typically used when the research participants are not physically present to sign a consent form and the study is minimal risk.
- Use of the HRP-502e Template Cover Letter is required, and the participant is given the opportunity to read the cover letter before deciding on participation in the research (see SOP HRP-090).
- Please see “CHECKLIST: Waiver or Alteration of the Consent Process (HRP-410)” and “CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)” for the requirements to qualify for the waiver.

How do I submit a modification?

Access the study and click the “Create Modification/CR” activity. Choose whether the modification involves an update of the study team only or contains other, non-study team related changes (this choice will allow changes to be made to the protocol and relevant attachments). Complete the Modification SmartForm in the ICON system and attach all requested supplementary documentation. Ensure the HRP-503 document is modified to include all changes. Submit the SmartForm by clicking the “Submit” activity. Maintain electronic copies of all information submitted to the IRB in case revisions are required. Please note that research must continue to be conducted as approved without the inclusion of the proposed changes until written IRB approval is received. Updates to the list of study personnel will be approved administratively by office staff unless the update represents the appointment of a new PI or further review is required for a potential conflict of interest. New personnel will not be approved until they have completed the CITI training requirement.

How do I submit continuing review?

Access the study and click the “Create Modification/CR” activity. Complete the Continuing Review SmartForm in the ICON system and attach any applicable supplementary documentation. Submit the SmartForm by clicking the “Submit” activity. Maintain electronic copies of all information submitted to the IRB in case revisions are required. Before submitting the research for continuing review, the PI or PI proxy must again:

- Ascertain whether any member of the research team has a financial interest related to the research. A “yes” or “no” answer is sufficient; there is no need to obtain additional financial details from a study team member. A “yes” answer will be referred to the research conflict of interest office for follow-up and review.
- Obtain the verbal or written agreement of each member of the research staff to his/her role in the research.

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If the continuing review involves modifications to previously approved research, an option is available to submit a “continuing review with modifications.” However, if the modification is complex, or the study is close to its IRB expiration date, it is strongly recommended to submit those modifications as a separate request following continuing review using the Modification SmartForm to avoid a lapse in approval.

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

What Happens if IRB Approval Expires?

If IRB approval of a human subjects research protocol expires, all research procedures related to the protocol must cease, including recruitment, advertisement, screening, enrollment, consent, interventions, interactions, and collection or analysis of private identifiable information.

Continuing research during a lapse in protocol approval is a violation of both federal and organizational policy. If current subjects may be harmed by stopping research procedures that are not available outside the research context, contact the IRB coordinator or Chair immediately and provide written justification stating how stopping Human Research procedures will negatively impact the subject. Provide a coded list of the currently enrolled subjects and a schedule of upcoming visits/procedures. The IRB will provide further direction.

If a faculty member anticipates leaving the institution before the next continuing review and the research will continue, the PI should consult with his/her Department to determine whether the study will be transferred to the new institution or if a new PI will be assigned to take responsibility for the research activities at UH. This decision must be consistent with requirements of the funding agency (if applicable) and should be communicated to the IRB office as soon as possible so the applicable changes can be made in ICON. All such changes must be made prior to the PI leaving the institution. Should human subjects research protocols remain open after a faculty PI leaves the institution, the Department will be responsible for closing or transferring responsibility for the protocol to another qualified PI. This could cause significant delays in the transfer of funds or interrupt the conduct of the study until the issue of responsibility is resolved.

How do I close out a study?

All studies should be formally closed once the research, including analysis of identifiable data, is complete. Click “Create Modification/CR” in ICON and select “Continuing Review.” If the first four Research Milestones boxes are checked in section 2 within the continuing review submission, the study will be closed pending final review by the IRB staff.

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How long do I keep records?

All records related to IRB-approved human subjects research, including signed and dated consent documents, must be securely maintained **on the UH campus or the UH server** for at least three years following completion of the research. While three years reflects the federal IRB requirement, always verify the length of time required to store data with the funding agency as well as any agency overseeing the research (e.g., U.S. Food and Drug Administration (FDA)), as these times may be significantly longer. Signed and dated HIPAA authorizations and consent documents that include HIPAA authorizations must be maintained for at least six years following completion of the research.

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

Contact the IRB Office 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 use, and make sure these are followed. Use the "Template Emergency Use Consent Template (HRP-506)" to prepare your consent document. You will need to submit a report of the use to the IRB within five days of the use and for drugs, devices and biologics, submit an IRB application for initial review within 30 days.

If you fail to submit the report within five days or the IRB application for initial review within 30 days, you will be restricted from submitting new Human Research until the report and IRB application for initial review has been received.

Emergency use of an unapproved drug or biologic in a life-threatening situation without prior IRB review is "research" as defined by the FDA. The individual getting the test article is a "subject" as defined by the FDA, and therefore is governed by the FDA regulations for IRB review and informed consent. Emergency use of an unapproved device without prior IRB review is not "research" as defined by the FDA. The individual getting the test article is not a "subject" as defined by the 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 DHHS defines that term.

How do I request reliance on another IRB?

Reliance agreements are arrangements between institutions allowing the IRB of one institution to rely on the IRB of another institution for review of collaborative or multi-site human subjects research.

All domestic sites participating in an NIH-funded multi-site research⁴ study are required

⁴ NIH References: http://osp.od.nih.gov/sites/default/files/sIRB_FAQs_Final_UPDATED2016.pdf,
<https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-094.html>

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to use a single IRB rather than obtaining local IRB approval from each individual site. This policy is applicable to sites conducting the same non-exempt human subjects research protocol supported through NIH grants, cooperative agreements, contracts, or the NIH Intramural Research Program. The policy does not apply to NIH career development, research training, or fellowship awards.

Common rule regulations at 45 CFR Part 46.114⁵ also require that any institution located in the United States engaged in cooperative research must rely upon approval by a single IRB for that portion of the research conducted in the United States. Reliance on another IRB requires an abbreviated submission in ICON and an agreement signed by both institutions acknowledging the reliance prior to beginning the research. The decision on which IRB will be the reviewing IRB is decided by the institutions' research offices; it is highly recommended to contact the IRB office during the grant-writing process to determine the most appropriate arrangement.

The University of Houston is a signatory on a reciprocity agreement with other Texas Medical Center (TMC) institutions and their affiliate institutions, meaning an abbreviated process is already in place to establish reliance agreements with these institutions. The UH IRB also works with Sterling IRB for industry-sponsored clinical trials, and with PEDIG for some pediatric optometry studies. Agreements may be put in place with other institutions or IRBs for other collaborative projects if the other institution has such a process in place. UH is not a signatory on SMART IRB at this time.

Investigators and institutions must conduct the research in accordance with the signed agreement, which should detail roles and responsibilities of each institution with regard to items such as training, conflicts of interest, communication between IRBs, reporting of adverse events, investigation of noncompliance, and reporting to federal and funding agencies.

Detailed, step-by-step guidance for requesting reliance on another IRB, or for another site to rely on the UH IRB, can be found on the IRB website reliance page:

<https://www.uh.edu/research/compliance/irb/irb-reliance/>

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 in the ICON library; selected items are also available on the IRB Web Site at <http://www.uh.edu/research/compliance/irb/policies/>

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

⁵ Common Rule References: [45 CFR 46](#)

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Research Integrity and Oversight (RIO)
316 E. Cullen Building, 4th floor
Houston, TX 77204-2015
Email: cphs@central.uh.edu
Main IRB office number: (713) 743-9204

Questions, concerns, complaints, allegations of undue influence, allegations or findings of non-compliance, or input regarding the Human Research Protection Program (HRPP) may be reported orally or in writing. Concerns may be reported to the IRB Chair, IRB Office, or Institutional Official (the Associate Vice President for Research and Technology Transfer, Dr. Claudia Neuhauser).

The IRB has the responsibility to investigate allegations of non-compliance and require corrective actions as needed. Faculty, staff, and students are permitted to report concerns on an anonymous basis using the [UH Fraud and Noncompliance hotline](#).

Employees who report in good faith possible compliance issues may not be subjected to retaliation or harassment due to the reporting. Concerns about possible retaliation should be immediately reported to the Vice President for Research and Technology Transfer.

Additional IRB Contacts:

Dr. Danielle Griffin
Associate Director, Research Integrity and Oversight (RIO)
Email: dgriffi5@central.uh.edu
(713) 743-4057

Ms. Kirstin M. Holzschuh
Executive Director, Research Integrity and Oversight (RIO)
Email: kmholzsc@central.uh.edu
(713) 743-9740

Dr. Claudia Neuhauser
Associate Vice Chancellor/Vice President for Research and Technology Transfer
Email: cmneuhau@central.uh.edu
(713) 743-6961

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Appendix A-1 ***Additional Requirements for DHHS-Regulated Research⁶***

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.

⁶ <http://www.hhs.gov/ohrp/policy/subjectwithdrawal.html>

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

1. When a subject withdraws from a study:⁷
 - a. The data collected on the subject to the point of withdrawal remains part of the study database and may not be removed.
 - b. An investigator may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review and address the maintenance of privacy and confidentiality of the subject's information.
 - c. If a subject withdraws from the interventional portion of the study but agrees to continued follow-up of associated clinical outcome information as described in the previous bullet, the investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). IRB approval of informed consent documents is required.
 - d. If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent.
 - e. An investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.
2. For FDA-regulated research involving investigational drugs:
 - a. Investigators must abide by FDA restrictions on promotion of investigational drugs:⁸
 - i. An investigator, or any person acting on behalf of an investigator, must not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug.
 - ii. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

⁷ <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126489.pdf>

⁸ <http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.7>

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- iii. An investigator must not commercially distribute or test market an investigational new drug.
- b. Follow FDA requirements for general responsibilities of investigators⁹
 - 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 drug¹⁰
 - 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 retention¹¹
 - i. Disposition of drug:
 - 1. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects.
 - 2. If the investigation is terminated, suspended, discontinued, or completed, the investigator must return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 21 CFR §312.59.
 - ii. Case histories.
 - 1. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation.
 - 2. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital charts, and the

⁹ <http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.60>

¹⁰ <http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.61>

¹¹ <http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.62>

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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 reports¹²
 - 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 review¹³
 - 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.

¹² <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.64>

¹³ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.66>

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- g. Follow FDA requirements for inspection of investigator's records and reports¹⁴
 - 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 substances¹⁵
 - i. If the investigational drug is subject to the Controlled Substances Act, the investigator must take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.
3. For FDA-regulated research involving investigational devices:
 - a. General responsibilities of investigators.¹⁶
 - 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 investigators¹⁷
 - i. Awaiting approval: An investigator may determine whether potential subjects would be interested in participating in an investigation but must not request the written informed consent of any subject to participate, and must not allow any subject to participate before obtaining IRB and FDA approval.
 - ii. Compliance: An investigator must conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.
 - iii. Supervising device use: An investigator must permit an investigational device to be used only with subjects under the

¹⁴ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=312.68>

¹⁵ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=312.69>

¹⁶ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=812.100>

¹⁷ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=812.110>

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investigator's supervision. An investigator must not supply an investigational device to any person not authorized to receive it.

- iv. Financial disclosure:
 - 1. A clinical investigator must disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required under 21 CFR §54.
 - 2. The investigator must promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.
- v. Disposing of device: Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator must return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.
- c. Maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:¹⁸
 - 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

¹⁸ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=812.140>

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investigation, including information about relevant previous medical history and the results of all diagnostic tests.

4. A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.
- iv. The protocol, with documents showing the dates of and reasons for each deviation from the protocol.
- v. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.
- d. Inspections¹⁹
 - 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 reports²⁰
 - 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.

¹⁹ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.145>

²⁰ <http://www.accessdata.fda.gov/SCRIPTS/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.150>

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- iv. Deviations from the investigational plan:
 1. An investigator must notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency.
 2. Such notice must be given as soon as possible, but in no event later than 5 working days after the emergency occurred.
 3. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB also is required.
- v. Informed consent. If an investigator uses a device without obtaining informed consent, the investigator must report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.
- vi. Final report. An investigator must, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.
- vii. Other. An investigator must, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

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

1. Investigator's Qualifications and Agreements
 - a. The clinical trial should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practice and the applicable regulatory requirements.
 - b. The investigator should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirements, and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB, and/or the regulatory authorities.
 - c. The investigator should be thoroughly familiar with the appropriate use of the investigational product, as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.
 - d. The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.
 - e. The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authorities.
 - f. The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.
2. Adequate Resources
 - a. The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.
 - b. The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.
 - c. The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
 - d. The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product, and their trial-related duties and functions.
3. Medical Care of Trial Subjects
 - a. A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.
 - b. During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illnesses of which the investigator becomes aware.

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- c. It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.
 - d. Although a subject is not obliged to give his/her reasons for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reasons, while fully respecting the subject's rights.
4. Communication with IRB
- a. Before initiating a trial, the investigator/institution should have written and dated approval opinion from the IRB for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.
 - b. As part of the investigator's/institution's written application to the IRB, the investigator/institution should provide the IRB with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB.
 - c. During the trial the investigator/institution should provide to the IRB all documents subject to review.
5. Compliance with Protocol
- a. The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authorities and which was given approval opinion by the IRB. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.
 - b. The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval opinion from the IRB of an amendment, except where necessary to eliminate an immediate hazard to trial subjects, or when the changes involves only logistical or administrative aspects of the trial (e.g., change in monitors, change of telephone numbers).
 - c. The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.
 - d. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to trial subjects without prior IRB approval opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendments should be submitted: a) to the IRB for review and approval opinion, b) to the sponsor for agreement and, if required, c) to the regulatory authorities.
6. Investigational Product
- a. Responsibility for investigational product accountability at the trial site rests with the investigator/institution.

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- b. Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product accountability at the trial site to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.
 - c. The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product. These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product received from the sponsor.
 - d. The investigational product should be stored as specified by the sponsor and in accordance with applicable regulatory requirements.
 - e. The investigator should ensure that the investigational product is used only in accordance with the approved protocol.
 - f. The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.
 - g. Randomization Procedures and Unblinding: The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product.
7. Informed Consent of Trial Subjects
- a. In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB's written approval opinion of the written informed consent form and any other written information to be provided to subjects.
 - b. The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB's approval opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that

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may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

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

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

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- xvii. The persons to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
- xviii. The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
- xix. The expected duration of the subject's participation in the trial.
- xx. The approximate number of subjects involved in the trial.
- k. Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.
- l. When a clinical trial (therapeutic or non-therapeutic) includes subjects, who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.
- m. Except as described 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.
- n. Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled: a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally. b) The foreseeable risks to the subjects are low. c) The negative impact on the subject's well-being is minimized and low. d) The trial is not prohibited by law. e) The approval opinion of the IRB is expressly sought on the inclusion of such subjects, and the written approval opinion covers this aspect. Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.
- o. In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval opinion by the IRB, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the

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trial as soon as possible and consent to continue and other consent as appropriate should be requested.

8. Records and Reports

- a. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- b. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.
- c. Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections. Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.
- d. The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirements. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.
- e. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.
- f. The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.
- g. Upon request of the monitor, auditor, IRB, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

9. Progress Reports

- a. The investigator should submit written summaries of the trial status to the IRB annually, or more frequently, if requested by the IRB.
- b. The investigator should promptly provide written reports to the sponsor, the IRB and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

10. Safety Reporting

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- a. All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirements related to the reporting of unexpected serious adverse drug reactions to the regulatory authorities and the IRB.
 - b. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.
 - c. For reported deaths, the investigator should supply the sponsor and the IRB with any additional requested information (e.g., autopsy reports and terminal medical reports).
 - d. Premature Termination or Suspension of a Trial If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirements, should inform the regulatory authorities. In addition:
 - i. If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB and should provide the sponsor and the IRB a detailed written explanation of the termination or suspension.
 - ii. If the sponsor terminates or suspends a trial, the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB and provide the IRB a detailed written explanation of the termination or suspension.
 - iii. If the IRB terminates or suspends its approval opinion of a trial, the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.
11. Final Reports by Investigator: Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the trial's outcome, and the regulatory authorities with any reports required.

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Appendix A-4

Additional Requirements for Department of Defense (DOD) research

1. When appropriate, research protocols must be reviewed and approved by the IRB prior to the Department of Defense approval. Consult with the Department of Defense funding component to see whether this is a requirement.
2. Employees of the Department of Defense (including temporary, part-time, and intermittent appointments) may not be able to legally accept payments to participate in research and should check with their supervisor before accepting such payments. Employees of the Department of Defense cannot be paid for conducting research while on active duty.
3. Service members must follow their command policies regarding the requirement to obtain command permission to participate in research involving human subjects while on-duty or off-duty.
4. Components of the Department of Defense might have stricter requirements for research-related injury than the DHHS regulations.
5. There may be specific educational requirements or certification required.
6. When assessing whether to support or collaborate with this institution for research involving human subjects, the Department of Defense may evaluate this institution's education and training policies to ensure the personnel are qualified to perform the research.
7. When research involves U.S. military personnel, policies and procedures require limitations on dual compensation:
 - a. Prohibit an individual from receiving pay 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.
8. Other specific requirements of the Department of Defense research be found in the "Additional Requirements for Department of Defense (DOD) Research" section in the IRB's "WORKSHEET: Additional Federal Criteria (HRP-318)."

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

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

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

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

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

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

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

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

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

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Requirements for Department of Justice (DOJ) Research” section in the IRB’s
“WORKSHEET: Additional Federal Criteria (HRP-318).”

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Appendix A-7

Additional Requirements for Department of Education (ED) Research

1. Each school at which the research is conducted must provide an assurance that they comply with the Family Educational Rights and Privacy Act (FERPA) and the Protection of Pupil Rights Amendment (PPRA).
2. Provide a copy of all surveys and instructional material used in the research. Upon request parents of children²¹ involved in the research²² must be able to inspect these materials.
3. The school in which the research is being conducted must have policies regarding the administration of physical examinations or screenings that the school may administer to students.
4. Other specific requirements of the Department of Education (ED) Research can be found in the “Additional Requirements for Department of Education (ED) Research” section in the IRB’s “WORKSHEET: Additional Federal Criteria (HRP-318).”

²¹ 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.

²² Research or experimentation program or project means any program or project in any research that is designed to explore or develop new or unproven teaching methods or techniques.

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

1. Research conducted, supported, or intended to be submitted to EPA is subject to Environmental Protection Agency Regulations.
2. Intentional exposure of pregnant women or children to any substance is prohibited.
3. Observational research involving pregnant women and fetuses are subject to additional DHHS requirements for research involving pregnant women (45 CFR §46 Subpart B) and additional DHHS requirements for research involving children (45 CFR §46 Subpart D.)
4. Research involving children must meet category #1 or #2.
5. Other specific requirements of the Environmental Protection Agency (EPA) Research can be found in the “Additional Requirements for Environmental Protection Agency (EPA) Research and Research Intended to be Submitted to the Environmental Protection Agency” section in the IRB’s “WORKSHEET: Additional Federal Criteria (HRP-318).”