Investigator Manual

Revised August 12, 2016

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Scope

Throughout this document "organization" refers to Roswell Park Cancer Institute.

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 does my staff and I need in order to conduct Human Research?"

What is Human Research?

The "HUMAN RESEARCH PROTECTION PROGRAM PLAN (HRP-101)" defines the activities that this organization considers to be "Human Research." An algorithm for determining whether an activity is Human Research can be found in the "WORKSHEET: Human Research (HRP-310)," located in the IRB Policies & Procedures section of the IRB Web site. 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 not to conduct Human Research without prior IRB review and approval (or a determination that a research project is either exempt Human Research or not Human Subject Research). If you have questions about whether an activity is Human Research, contact the Office of Research Subject Protection (ORSP) who will provide you with a determination. If you wish to have a written determination, provide a written request to the ORSP.

What is the Human Research Protection Program?

The document "HUMAN RESEARCH PROTECTION PROGRAM PLAN (HRP-101)" describes this organization's overall plan to protect subjects in Human Research.

- The mission of the Human Research Protection Program.
- The ethical principles that the organization follows governing the conduct of Human Research.
- The applicable laws that govern Human Research.
- When the organization becomes "engaged in Human Research" and when someone is acting as an agent of the organization conducting Human Research.
- Clinical Research Services involvement in clinical research implemented at RPCI
- The types of Human Research that may not be conducted.
- The roles and responsibilities of individuals within the organization.

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

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

Investigators and staff conducting human research must complete the Collaborative Institutional Training Initiative (CITI) human subjects protection online training program. .

Investigators and research staff of human research studies that are FDA-regulated (i.e., involving drugs, biologics or medical devices) and more than minimal risk must also complete a Good Clinical Practices course in the CITI program.

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

Training is valid for a three-year period, after which time the training must be repeated. Investigators who do not complete renewal of the training prior to the three-year expiration will be restricted from submitting new studies or from being added to existing studies until the training is completed. Ongoing studies may be suspended or terminated; restricted co-investigators will be removed if renewal of the training is not completed within a reasonable manner after the three-year expiration as the Director of Research Subject Protection deems appropriate.

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

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

All individuals involved in the design, conduct, or reporting of research are required to disclose the financial interests:

- 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.

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

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

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

Additional details can be found in “SOP: Financial Conflicts of Interests (HRP-055).”

How do I submit new Human Research to the IRB?

Biospecimen/Data Research are submitted directly to the ORSP. When review by the Scientific Review Committee (SRC) is required, all documents, including any requested clarifications from the SRC and their resolution, will be submitted with the application for review to the Office of Research Subject Protection.

Complete the New Study SmartForm in the electronic Click system and attach all requested supplements; the SmartForm is submitted by the PI by clicking the "Submit" activity. By clicking Submit the is PI verifying that:

- You have obtained the financial interest status of each research staff.
- You have obtained the agreement of each research staff to his/her role in the research.
- You will conduct this Human Research in accordance with requirements in the HRP-103 - Investigator Manual

How do I submit new Human Research that will be covered by an External IRB?

It is the policy of the RPCI IRB to provide protection for human subjects participating in research protocols at RPCI. The RPCI IRB may agree for an external IRB to be the IRB of record for certain human research studies. The RPCI IRB must be notified of each study to be conducted at RPCI that proposes to use an external IRB prior to study initiation. An IRB Authorization Agreement / Division of Responsibilities must be executed with the Institutional Official for studies that will be relying on an external IRB. The ORSP will maintain oversight of local informed consent content, assuring compliance with local policies and procedures and HIPAA regulations, as well as other local context issues to assure safe and appropriate conduct of the research.

The Initial Study, any Modifications, and Continuing Reviews must be submitted in the electronic Click system after approval by the external IRB and prior to implementation at RPCI. The ORSP will review the submission and determine whether any clarifications are required prior to accepting the external IRB's approval. Reportable New Information must be submitted in the electronic Click system within five business days of submission to the external IRB.

How do I write an Investigator Protocol?

Use the "TEMPLATE PROTOCOL (HRP-503)" as a starting point for drafting a new Investigator Protocol, and reference the instructions in italic text for the information the IRB looks for when reviewing research. Intervention studies determined to be high priority will recommend protocol editor support at time of Clinical Research Prioritization& Feasibility review.

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

- The italicized bullet points in the "TEMPLATE PROTOCOL (HRP-503)"" serve as guidance to investigators when developing an Investigator Protocol for submission to the IRB. All italicized text are meant to be deleted prior to submission.
- When writing an Investigator Protocol, always keep an electronic copy. You will need to modify this copy when making changes to the Investigator Protocol.
- If you believe your activity may not be Human Research, contact the ORSP prior to developing your Investigator Protocol.

- Note that, depending on the nature of your research, certain sections of the template may not be applicable to your Investigator Protocol. Indicate this as appropriate.
- You may not involve any individuals who are members of the following populations as subjects in your research unless you indicate this in your inclusion criteria as the inclusion of subjects in these populations has regulatory implications.
    - Adults unable to provide legally effective consent as a targeted population
    - Individuals who are not yet adults (infants, children, teenagers)
    - Pregnant women (Note: Roswell Park Cancer Institute does not conduct research with pregnant women as a specific study population unless the research holds out a prospect of direct benefit to the individual participant.)
    - Prisoners (Note: Roswell Park Cancer Institute does not conduct research with prisoners as a specific study population, but does not prohibit prisoners from enrolling in a research study if certain conditions are met)
- If you are conducting community-based participatory research, you may contact the ORSP for information about:
    - Research studies using a community-based participatory research design
    - Use of community advisory boards
    - Use of participant advocates
    - Partnerships with community-based organizations

How do I create a consent document?

Use the "TEMPLATE CONSENT DOCUMENT (HRP-502)" to create a consent document.

Note that all long form consent documents and all summaries for short form consent documents must contain all of the required and all additional appropriate elements of informed consent disclosure. 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 the short form of consent documentation the appropriate signature block from "TEMPLATE CONSENT DOCUMENT (HRP-502)" should be used on the short form.

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

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

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

- Not "Human Research": Activities must meet the organizational definition of "Human Research" to fall under IRB oversight. Activities that do not meet this definition are not subject to IRB oversight but are reviewed by the ORSP. Review the ORSP's "WORKSHEET: Human Research (HRP-310)" for reference. Contact the ORSP in cases where it is unclear whether an activity is Human Research.

- Exempt: Certain categories of Human Research may be exempt from certain regulations and from IRB review. It is the responsibility of the ORSP, not the investigator, to determine whether Human Research is exempt from IRB review. Review the ORSP's "WORKSHEET: Exemption (HRP-312)" for reference on the categories of research that may be exempt.
- Review Using the Expedited Procedure: Certain categories of non-exempt Human Research may qualify for review using the expedited procedure, meaning that the project may be approved by a single designated IRB reviewer, rather than the convened board. Review the IRB Administration's "WORKSHEET: Eligibility for Review Using the Expedited Procedure (HRP-313)" for reference on the categories of research that may be reviewed using the expedited procedure.
- Review by the Convened IRB: Non-Exempt Human Research that does not qualify for review using the expedited procedure must be reviewed by the convened IRB.

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

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

- Approval: Made when all criteria for approval are met. See "How does the IRB decide whether to approve Human Research?" below.
- Modifications Required to Secure Approval: Made when IRB members require specific modifications to the research before approval can be finalized.
- Tabled: Made when the IRB cannot approve the research at a meeting for reasons unrelated to the research, such as loss of quorum. When taking this action, the IRB automatically schedules the research for review at the next meeting.
- Deferred: Made when the IRB determines that the board is unable to approve research and the IRB suggests modifications that might make the research approvable. When making this motion, the IRB describes its reasons for this decision, describes modifications that might make the research approvable, and gives the investigator an opportunity to respond to the IRB in person or in writing.
- Disapproval: Made when the IRB determines that it is unable to approve research and the IRB cannot describe modifications that might make the research approvable. When making this motion, the IRB describes its reasons for this decision and gives the investigator an opportunity to respond to the IRB in person or in writing.

How does the IRB decide whether to approve Human Research?

The criteria for IRB approval can be found in the "WORKSHEET: Criteria for Approval (HRP-314)" for non-exempt Human Research. This worksheet references other checklists that might be relevant. All checklists and worksheets can be found on the IRB block on the i2.

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.

The criteria for ORSP to make an exempt human research determination can be found in "WORKSHEET: Exemption (HRP-312)".

What will happen after IRB review?

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

- If the IRB has approved the Human Research: The Human Research may commence once all other organizational approvals have been met. IRB approval is usually good for a limited period of time which is noted in the approval letter.
- If the IRB requires modifications to secure approval and you accept the modifications: Make the requested modifications and submit them to the IRB. If all requested modifications are made, the IRB will issue a final approval. Research cannot commence until this final approval is received. If you do not accept the modifications, provide your response and submit it to the IRB for review.
- If the IRB defers the Human Research: The IRB will provide a statement of the reasons for deferral and suggestions to make the study approvable, and give you an opportunity to respond in writing. In most cases if the IRB's reasons for the deferral are addressed in a modification, the Human Research can be approved
- If the IRB disapproves the Human Research: The IRB will provide a statement of the reasons for disapproval and give you an opportunity to respond in writing.

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

What are my obligations after IRB approval?

1) Do not start Human Research activities until you have the final IRB approval letter and the study is activated and posted on the Clinical Studies internal website (Https: clinical studies.roswellpark.org)
2) Do not start Human Research activities until you have obtained all other required institutional approvals, including approvals of departments or divisions that require approval prior to commencing research that involves their resources.
3) Ensure that there are adequate resources to carry out the research safely. This includes, but is not limited to, sufficient investigator time, appropriately qualified research team members, equipment, and space.
4) Ensure that Research Staff are qualified (e.g., including but not limited to appropriate training, education, expertise, credentials, protocol requirements and, when relevant, privileges) to perform procedures and duties assigned to them during the study.
5) Update the ORSP with any changes to the list of study personnel.
6) Personally conduct or supervise the Human Research. Recognize that the investigator is accountable for the failures of any study team member.
   a) Conduct the Human Research in accordance with the relevant current protocol as approved by the IRB, and in accordance with applicable federal regulations and local laws.
   b) When required by the IRB ensure that consent or permission is obtained in accordance with the relevant current protocol as approved by the IRB.

c) Do not modify the Human Research without prior IRB review and approval unless necessary to eliminate apparent immediate hazards to subjects.
d) Protect the rights, safety, and welfare of subjects involved in the research.

7) Submit to the IRB:
   a) Proposed modifications as described in this manual. (See "How do I submit a modification?")
   b) A continuing review application as requested in the approval letter. (See "How do I submit continuing review?"
   c) Report of premature completion of study (See "How Do I Close a Study?)
   d) A final continuing review application when the Human Research is closed. (See "How Do I Close Out a Study?")
8) Report any of the information items on the back of "FORM: Reportable New Information (HRP-214)" to the IRB within five business days.
9) Submit an updated disclosure of financial interests within thirty days of discovering or acquiring (e.g., through purchase, marriage, or inheritance) a new financial interest.
10) Do not accept or provide payments to professionals in exchange for referrals of potential subjects ("finder's fees.")
11) Do not accept payments designed to accelerate recruitment that were tied to the rate or timing of enrollment ("bonus payments.")
12) See additional requirements of various federal agencies in Appendix A. These represent additional requirements and do not override the baseline requirements of this section.

How do I document consent?

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

The following are the requirements for long form consent documents:

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

The following are the requirements for short form consent documents:

- The subject or representative signs and dates the short form consent document .
- The individual obtaining consent signs and dates the summary.
- The witness to the oral presentation signs and dates the short form consent document and the summary.
- Copies of the signed and dated short form consent document and summary are provided to the subject or representative.

How do I submit a modification?

Complete the Modification SmartForm in the electronic Click system and attach all requested supplements; the SmartForm is submitted by the PI 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 without inclusion of the modification until IRB approval is received. Updates to the list of study personnel will be acknowledged unless the update represents a modification to the research.

How do I submit continuing review?

Complete the Continuing Review SmartForm in the electronic IRB system and attach all requested supplements; the SmartForm is submitted by the PI by clicking the "Submit" activity. Maintain electronic copies of all information submitted to the IRB in case revisions are required. Before submitting the continuing review, you must:

- Determine whether any co-investigator or member of the research staff has a financial interest related to the research. A "yes" or "no" answer is sufficient. There is no need to obtain additional details.

Changes to study staff and consent modifications are allowed at the time of continuing review. If the continuing review involves modifications to previously approved research (changes other than consent or study staff), submit those modifications as a separate request for modification using the Modification SmartForm in the electronic Click system.

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

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

What is the process for study suspension or termination by others

Suspension or Termination **not** initiated by the IRB
In addition to the IRB, the following are authorized to suspend or terminate research on an urgent basis.

- Principal Investigator
- Sponsor
- IRB, Chair or board designee
- Appropriate Organizational Officials (Institute Official Chief Executive Officer, Senior Vice President of Clinical Investigations)
- Regulatory Agencies

The authorized party will notify ORSP who will follow up with research team to ensure that actions representing unanticipated problems or adverse outcomes are reported to the IRB. All other actions will be reported at the next convened IRB meeting.

Considerations for Suspension or Termination
The convened IRB or other person ordering the suspension or termination shall:

- Consider actions to protect the rights and welfare of currently enrolled subjects such as:
  - o Making arrangements for medical care off a research study;
  - o Transfer to another investigator;
  - o Continuation in the research under independent monitoring
- Consider whether subjects should be informed of the termination or suspension
- Consider continued adverse event or outcomes reporting to the IRB.

Reporting:
Reporting of suspensions and terminations to regulatory agencies and appropriate organizational officials will be done per the HRP 101 Human Research Subject Protect Plan, "Special reporting requirements and procedures of IRB Findings

How do I close out a study?

Immediate notice of study closure can be submitted via the Report New Information activity in Click. To formally close out a study, complete the Continuing Review SmartForm in the electronic Click system and attach all requested supplements; the SmartForm is submitted by the PI by clicking the "Submit" activity. Maintain electronic copies of all information submitted to the IRB in case revisions are required.

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

If the final continuing review application for closing out a Human Research study is not received by the date requested in the approval letter, you will be restricted from submitting new Human Research until the completed application is received.

How long do I keep records?

Maintain your Human Research records, including signed and dated consent documents for at least six years after completion of the research. Maintain signed and dated HIPAA authorizations and consent documents that include HIPAA authorizations for at least six years after completion of the research.

If your Human Research is sponsored contact the sponsor before disposing of Human Research records.

What if I want to treat a single patient with an unapproved drug, biologic or device through the use of a compassionate exemption (CE)?

Contact the ORSP to inform them that a compassionate exemption is being considered for the treatment of a patient.

***Do not schedule the patient for treatment before IRB approval is received**.

The ORSP will assemble an IRB meeting in order to review the application. The committee will be convened as soon as practicable within 24 - 72 hours of the request.

REQUIRED DOCUMENTATION:

1. F-137a form is to be completed.
2. Complete the rationale/justification and risk/benefit assessment form for the treatment proposed. Be sure to explain why standard treatment is not indicated for this patient.
3. Submit a treatment protocol that is the basis for the treatment. Treatment drugs, doses, routes, and schedule must be given in detail and justified based on published/unpublished experience.
4. Submit a proposed consent (use RPCI model template)
5. Provide recent clinic notes from referring or treating physicians.

With a quorum and majority vote on the request, the ORSP will notify the treating physician of the committee's decision. When the board is convened for Compassionate use, quorum will be defined as at least 5 members from existing RPCI IRBs. Minimally, there must be at least 5 registered IRB members of varying background and expertise to execute a thorough review of the proposal and will include at least one member with a non-scientific background and one member who is unaffiliated with the Institute.

If approved, the compassionate exemption approval and the stamped consent are released by the ORSP to the investigator. Only this consent can be used to consent the patient. ORSP will also facilitate submission to the FDA when applicable. Treatment of the patient cannot be initiated until the FDA has granted approval.

After obtaining the signature of the patient, the physician, and the witness (if applicable), a copy of the signed consent document should be forwarded to the ORSP.

Within FIVE (5) days of treatment under the compassionate exemption, you are required to submit an interim report to the ORSP summarizing the initial treatment of the patient with the unapproved drug, biologic or device, which will be provided to the IRB at the next scheduled meeting.

At termination of the therapy, you are required to submit a final report to the ORSP for submission to the FDA, if RPCI is the IND/IDE holder. A copy will be provided to the IRB at the next scheduled meeting.

All compassionate requests whether approved or not, are reported to the IRB at the next fully convened IRB meeting.

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

Contact the ORSP or IRB chair immediately to discuss the situation. If there is no time to make this contact, see the "WORKSHEET: Emergency Use (HRP-322)" for the regulatory criteria allowing such a use and make sure these are followed. Use the "TEMPLATE EMERGENCY USE CONSENT DOCUMENT (HRP-506)" to prepare your consent document. You will need to submit a report of the use to the IRB within

five days of the use and for drugs and biologics, submit an IRB application for initial review within 30 days.

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

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

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

How do I get additional information and answers to questions?

This document and the policies and procedures for the Human Research Protection Program are available on the IRB block on the i2.

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

Donald Handley
Administrative Director, Research Subject Protection and Scientific Integrity
Roswell Park Cancer Institute
Elm and Carlton Streets
Buffalo, NY 14263
Phone: 716.845.3455
Email: Donald.Handley@RoswellPark.org

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

Appendix A-1 ***Additional Requirements for DHHS-Regulated Research***[1]

1. When a subject decides to withdraw from a clinical trial, the investigator conducting the clinical trial should ask the subject to clarify whether the subject wishes to withdraw from all components of the trial or only from the primary interventional component of the trial. If the latter, research activities involving other components of the clinical trial, such as follow-up data collection activities, for which the subject previously gave consent may continue. The investigator should explain to the subject who wishes to withdraw the importance of obtaining follow-up safety data about the subject.
2. Investigators are allowed to retain and analyze already collected data relating to any subject who chooses to withdraw from a research study or whose participation is terminated by an investigator without regard to the subject's consent, provided such analysis falls within the scope of the analysis described in the IRB-approved protocol. This is the case even if that data includes identifiable private information about the subject.
3. For research not subject to regulation and review by FDA, investigators, in consultation with the funding agency, can choose to honor a research subject's request that the investigator destroy the subject's data or that the investigator exclude the subject's data from any analysis.
4. When seeking the informed consent of subjects, investigators should explain whether already collected data about the subjects will be retained and analyzed even if the subjects choose to withdraw from the research.

[1] http://www.hhs.gov/ohrp/policy/subjectwithdrawal.html

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

1. When a subject withdraws from a study:[2]
    a. The data collected on the subject to the point of withdrawal remains part of the study database and may not be removed.
    b. An investigator may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.
    c. If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information as described in the previous bullet, the investigator must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). IRB approval of informed consent documents is required.
    d. If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent.
    e. An investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.
2. For FDA-regulated research involving investigational drugs:
    a. Investigators must abide by FDA restrictions on promotion of investigational drugs:[3]
        i. An investigator, or any person acting on behalf of an investigator, must not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug.
        ii. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.
        iii. An investigator must not commercially distribute or test market an investigational new drug.
    b. Follow FDA requirements for general responsibilities of investigators[4]
        i. An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and

[2] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126489.pdf
[3] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.7
[4] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.60

applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

ii. An investigator must, in accordance with the provisions of 21 CFR §50, obtain the informed consent of each human subject to whom the drug is administered, except as provided in 21 CFR §50.23 or §50.24 of this chapter.

iii. Additional specific responsibilities of clinical investigators are set forth in this part and in 21 CFR §50 and 21 CFR §56.

c. Follow FDA requirements for control of the investigational drug[5]

i. An investigator must administer the drug only to subjects under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator.

ii. The investigator must not supply the investigational drug to any person not authorized under this part to receive it.

d. Follow FDA requirements for investigator recordkeeping and record retention[6]

i. Disposition of drug:

1. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects.
2. If the investigation is terminated, suspended, discontinued, or completed, the investigator must return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 21 CFR §312.59.

ii. Case histories.

1. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation.
2. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital charts, and the nurses' notes. The case history for each individual must document that informed consent was obtained prior to participation in the study.

iii. Record retention: An investigator must retain required records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

e. Follow FDA requirements for investigator reports[7]

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,

[5] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.61
[6] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.62
[7] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.64

the drug. If the adverse effect is alarming, the investigator must report the adverse effect immediately.

iii. Final report: An investigator must provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation.

iv. Financial disclosure reports:

1. The clinical investigator must provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under 21 CFR §54.
2. The clinical investigator must promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

f. Follow FDA requirements for assurance of IRB review[8]

i. An investigator must assure that an IRB that complies with the requirements set forth in 21 CFR §56 will be responsible for the initial and continuing review and approval of the proposed clinical study.

ii. The investigator must also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

g. Follow FDA requirements for inspection of investigator's records and reports[9]

i. An investigator must upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to 312.62.

ii. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

h. Follow FDA requirements for handling of controlled substances[10]

i. If the investigational drug is subject to the Controlled Substances Act, the investigator must take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

3. For FDA-regulated research involving investigational devices:

a. General responsibilities of investigators.[11]

i. An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA

[8] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.66
[9] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.68
[10] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.69
[11] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.100

regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with 21 CFR §50.

b. Specific responsibilities of investigators[12]
    i. Awaiting approval: An investigator may determine whether potential subjects would be interested in participating in an investigation, but must not request the written informed consent of any subject to participate, and must not allow any subject to participate before obtaining IRB and FDA approval.
    ii. Compliance: An investigator must conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.
    iii. Supervising device use: An investigator must permit an investigational device to be used only with subjects under the investigator's supervision. An investigator must not supply an investigational device to any person not authorized to receive it.
    iv. Financial disclosure:
        1. A clinical investigator must disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required under 21 CFR §54.
        2. The investigator must promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.
    v. Disposing of device: Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator must return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.

c. Maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:[13]
    i. All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.
    ii. Records of receipt, use or disposition of a device that relate to:
        1. The type and quantity of the device, the dates of its receipt, and the batch number or code mark.
        2. The names of all persons who received, used, or disposed of each device.
        3. Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.
    iii. Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example,

[12] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.110
[13] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.140

progress notes of the physician, the individual's hospital charts, and the nurses' notes. Such records must include:

1. Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent.
2. Documentation that informed consent was obtained prior to participation in the study.
3. All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
4. A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.

iv. The protocol, with documents showing the dates of and reasons for each deviation from the protocol.

v. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

d. Inspections[14]

i. Entry and inspection: A sponsor or an investigator who has authority to grant access must permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept).

ii. Records inspection: A sponsor, IRB, or investigator, or any other person acting on behalf of such a person with respect to an investigation, must permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation.

iii. Records identifying subjects: An investigator must permit authorized FDA employees to inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.

e. Prepare and submit the following complete, accurate, and timely reports[15]

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.

[14] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.145
[15] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.150

ii. Withdrawal of IRB approval. An investigator must report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.

iii. Progress. An investigator must submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.

iv. Deviations from the investigational plan:
    1. An investigator must notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency.
    2. Such notice must be given as soon as possible, but in no event later than 5 working days after the emergency occurred.
    3. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB also is required.

v. Informed consent. If an investigator uses a device without obtaining informed consent, the investigator must report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.

vi. Final report. An investigator must, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.

vii. Other. An investigator must, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

Appendix A-3 ***Additional Requirements for 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. Initial and continuing research ethics education is required for all personnel who conduct, review, approve, oversee, support or manage human research supported by the DoD or its components.
6. RPCI policy requires initial and continuing education of research personnel and IRB members every three (3) years.
7. Individual DoD components may have stricter or specific educational requirements. Researchers should contact their project coordinator at the DoD, or DoD component, to ensure adherence to any unique requirements.
8. The DoD component may also evaluate RPCI's education policies to ensure that personnel are qualified to perform the research, based on the complexity and risk of the research
9. There may be specific educational requirements or certification required.
10. 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.
11. 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.
12. 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)."

Appendix A-4 ***Additional Requirements for Department of Energy (DOE) Research***

1. Research that involves one or more of the following is considered by DOE to be human subjects research and requires IRB review:
    a. Intentional modification of the human environment
    b. Study of human environments that use tracer chemicals, particles or other materials to characterize airflow.
    c. Study in occupied homes or offices that:
        i. Manipulate the environment to achieve research aims.
        ii. Test new materials.
        iii. Involve collecting information on occupants' views of appliances, materials, or devices installed in their homes or their energy-saving behaviors through surveys and focus groups.
2. You must complete and submit to the IRB the DOE "Checklist for IRBs to Use in Verifying that HS Research Protocols are In Compliance with DOE Requirements" (http://human subjects.energy.gov/other-resources/documents/IRB-template-for-reviewing-PII-protocols-2010_ac.pdf) if your research includes Personally Identifiable Information. Please indicate with each item in the checklist where this is addressed within the protocol you have submitted to the IRB for review.
3. You must report the following within ten business days to the Department of Energy human subjects research program manager:
    a. Any signification 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.
4. 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.
5. Research involving human participants also includes studies of the intentional modification of the human environment; generalizable includes the study of tracer chemical, particles or other materials to characterize airflow.
6. Generalizable also includes studies in occupied home or offices that:
    a. Manipulate the environment to achieve research aim;
    b. Test new materials;
    c. Involve collecting information on occupants' views of appliances, materials; or
    d. Devices installed in their homes or their energy-saving behaviors through surveys and focus groups.

    Generalizable should be viewed in terms of the contribution to knowledge with the specific field of study.
7. Other specific requirements of the Department of Energy (DOE) research can be found in the "Additional Requirements for Department of Energy (DOE) Research" section in the IRB's "WORKSHEET: Additional Federal Criteria (HRP-318)."

Appendix A-5 ***Additional Requirements for Department of Justice (DOJ) Research***

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

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

investigator may not guarantee confidentiality when the subject indicates intent to commit future criminal conduct or harm himself or herself or someone else, or, if the subject is an inmate, indicates intent to leave the facility without authorization.

e. A statement that participation in the research project will have no effect on the inmate subject's release date or parole eligibility.

13. You must have academic preparation or experience in the area of study of the proposed research.
14. The IRB application must include a summary statement, which includes:
    a. Names and current affiliations of the investigators.
    b. Title of the study.
    c. Purpose of the study.
    d. Location of the study.
    e. Methods to be employed.
    f. Anticipated results.
    g. Duration of the study.
    h. Number of subjects (staff or inmates) required and amount of time required from each.
    i. Indication of risk or discomfort involved as a result of participation.
15. The IRB application must include a comprehensive statement, which includes:
    a. Review of related literature.
    b. Detailed description of the research method.
    c. Significance of anticipated results and their contribution to the advancement of knowledge.
    d. Specific resources required from the Bureau of Prisons.
    e. Description of all possible risks, discomforts, and benefits to individual subjects or a class of subjects, and a discussion of the likelihood that the risks and discomforts will actually occur.
    f. Description of steps taken to minimize any risks.
    g. Description of physical or administrative procedures to be followed to: Ensure the security of any individually identifiable data that are being collected for the study.
    h. Destroy research records or remove individual identifiers from those records when the research has been completed.
    i. Description of any anticipated effects of the research study on organizational programs and operations.
    j. Relevant research materials such as vitae, endorsements, sample consent statements, questionnaires, and interview schedules.
16. The IRB application must include a statement regarding assurances and certification required by federal regulations, if applicable.
17. You must assume responsibility for actions of any person engaged to participate in the research project as an associate, assistant, or subcontractor.
18. At least once a year, you must provide the Chief, Office of Research and Evaluation, with a report on the progress of the research.
19. At least 12 working days before any report of findings is to be released, you must distribute one copy of the report to each of the following: the chairperson of the Bureau Research Review Board, the regional director, and the warden of each institution that provided data or assistance.
20. You must include an abstract in the report of findings.

21. In any publication of results, you must acknowledge the Bureau's participation in the research project.
22. You must expressly disclaim approval or endorsement of the published material as an expression of the policies or views of the Bureau.
23. Prior to submitting for publication the results of a research project conducted under this subpart, You must provide two copies of the material, for informational purposes only, to the Chief, Office of Research and Evaluation, Central Office, Bureau of Prisons.
24. Other specific requirements of the Department of Justice (DOJ) Research Conducted within the Federal Bureau of Prisons (BOP) can be found in the "Additional Requirements for Department of Justice (DOJ) Research Conducted within the Federal Bureau of Prisons (BOP)" section in the IRB's "WORKSHEET: Additional Federal Criteria (HRP-318)."

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

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

Appendix A-6 ***Additional Requirements for Department of Education (ED) Research***

1. Each school at which the research is conducted must provide an assurance that they comply with the Family Educational Rights and Privacy Act (FERPA) and the Protection of Pupil Rights Amendment (PPRA).
2. Provide a copy of all surveys and instructional material used in the research. Upon request parents of children[16] involved in the research[17] must be able to inspect these materials.
3. The school in which the research is being conducted must have policies regarding the administration of physical examinations or screenings that the school may administer to students.
4. Other specific requirements of the Department of Education (ED) Research can be found in the "Additional Requirements for Department of Education (ED) Research" section in the IRB's "WORKSHEET: Additional Federal Criteria (HRP-318)."

[16] Children are persons enrolled in research not above the elementary or secondary education level, who have not reached the age or majority as determined under state law.

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

Appendix A-7 ***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)."