Investigator Manual[1]

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[1] This document satisfies AAHRPP element I.1.A, I.1.C-I.1.E, I-3, I.4.C, I.5.C, I.5.D, I.6.B, I.7.A-I.7.C, I-9, II.2.A, II.2.C, II.2.G, II.2.E-II.2.E.2, II.2.F-II.2.F.3, II.2.I, II.3.C-II.3.C.1, II.3.E, II.3.F, II.3.G, II.4.A, II.4.B, II.5.A, II.5.B, III.1.A, III.1.B, III.1.D, III.1.E, III.1.F, III.2.A, III.2.C, III.2.D

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NOTE: All referenced "HRP" documents can be found in the eIRB2 Library.

1. Scope

Throughout this document "organization" refers to Nationwide Children's Hospital, Inc. and all of its affiliates under the Nationwide Children's Hospital Federalwide Assurance as well as studies relying on the NCH sIRB where no other SOPs are stipulated in reliance documentation.

2. 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?"

3. What is Human Research?

The "HUMAN RESEARCH PROTECTION PROGRAM PLAN (HRP-101)" located in Library > General section of the eIRB2 Website 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)" and "Determination of Research Request Form", located in Library > General section of the eIRB2 Web site. Use these documents for guidance as to whether an activity meets either the DHHS or FDA definition of Human Research. The project PI can determine if a project meets the definition of research with these tools. The IRB strongly recommends that a determination of human subject research be submitted through a New Study application (SmartForm) in the electronic IRB system. Only the IRB can make the ultimate determination in questionable cases as to whether an activity constitutes Human Research subject to IRB oversight.

You should not conduct Human Research without prior IRB review and approval.

4. What is the Human Research Protection Program?

The document "HUMAN RESEARCH PROTECTION PROGRAM PLAN (HRP-101)" located in Library > General section of the eIRB2 Website describes this organization's overall plan to protect subjects in Human Research.

- The mission of the Human Research Protection Program.
- The ethical principles that the organization follows governing the conduct of Human Research.
- The applicable laws that govern Human Research.

- When the organization becomes "engaged in Human Research" and when someone is acting as an agent of the organization conducting Human Research.
- The types of Human Research that may not be conducted.
- The roles and responsibilities of individuals within the organization.

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

This section describes the training requirements required by the IRB. You may have additional training required by other federal, state, or organizational policies (refer to your Training Tracker account, "What Training Do I Need?").

Investigators and staff conducting research involving no more than minimal risk to subjects must complete the online CITI Human Subjects Protection course. Investigators and staff conducting research involving more than minimal risk to subjects must complete the online CITI Human Subjects Protection course plus the online CITI course, Effective Clinical Research Management. Investigators and staff conducting research involving drugs or devices must complete the CITI Good Clinical Practices (GCP) online course in addition to the two human subject courses.

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.

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.

See Training Tracker for other optional human research training courses.

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

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

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

Refer to "SOP: Financial Conflicts of Interests (HRP-055)" and the Research Institute's Policies and Procedures – Research – Compliance – 003-03, Research Conflict of Interest".

7. How do I submit new Human Research to the IRB?

- Complete the New Study SmartForm in the electronic IRB system and attach all requested supplements. BE SURE TO CHECK ALL APPLICABLE ANCILLARY REVIEWERS. See "Manage Ancillary Reviewers" link in the left column. Review Worksheet HRP-309 to determine which ancillaries are appropriate for your study.
- Have the SmartForm submitted by the PI (or PI Proxy) 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 initial review, you must:
  - Satisfy Conflict of Interest Disclosure requirements (all engaged research staff).
  - Satisfy all required training (all engaged research staff).
  - Obtain the agreement of research staff to his/her role in the research.

8. How do I request to rely on an external IRB?

Contact IRB.Reliance@nationwidechildrens.org for instructions.

9. How do I request that this IRB serve as the IRB of record (sIRB) for my collaborative or multi-site research study?

Contact IRB.Reliance@nationwidechildrens.org for instructions.

10. How do I write an Investigator Protocol?

A sponsor provided protocol can be submitted with your New Study SmartForm along with the "SITE SUPPLEMENT TO SPONSOR PROTOCOL (HRP-508)" form.

If you do not have a protocol, use the "HRP-503 TEMPLATE PROTOCOL" or "HRP-580 - NCH TEMPLATE SHORT PROTOCOL" as a guide for drafting a new Investigator Protocol The first page provides instructions regarding completion of protocol and how to submit when completed. Also, there are helpful tips throughout the templates regarding the information the IRB looks for when reviewing research. Here are some key points to remember when developing an Investigator Protocol:

- The bullet points in the "TEMPLATE PROTOCOL (HRP-503/HRP580)" serve as guidance to investigators when developing an Investigator Protocol for submission to the IRB.
- For any items described in other documents submitted with the application, investigators may simply reference these documents within the Investigator Protocol rather than repeat information.

- When writing an Investigator Protocol, always keep an electronic copy. You will need to modify this copy when making changes to the Investigator Protocol. Be sure to always include a version number/date on your protocol, but do not remove the IRB template name and date when doing so.
- If you believe your activity may not be Human Research, refer to WORKSHEET: Human Subject Determination (HRP-310) and the "Determination of Research Request Form" located in the Library > General section of the eIRB2 Web site. If you still have questions, contact the IRB Office at IRB@nationwidechildrens.org 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 by explaining why it is not appropriate. Do not simply enter N/A and do not delete sections of the protocol template.
- 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
    - Individuals who are not yet adults (infants, children, teenagers)
    - Pregnant women
    - Prisoners
- If you are conducting community-based participatory (planned emergency) research, you may contact the IRB Office for information about:
    - Research studies using a community-based participatory research design
    - Use of community advisory boards
    - Use of participant advocates
    - Partnerships with community-based organizations

11. What about a case study or case series?

Ordinarily a case report involves one or two cases. A case series will involve more. All case series must be reviewed and approved by the IRB.

For a case report (1-2 cases), an investigator does **not** need prior IRB review and approval if: (a) the records accessed are available to the investigator for clinical reasons (i.e., they or direct colleagues were involved in the care of this patient), (b) the records being reviewed contain data that were collected as part of routine clinical care (i.e., this policy does not deal with the use of existing research databases), and (c) the data are reviewed in a retrospective manner (because knowing upfront that a case report may be written could potentially lead to additional evaluations

being done which would not have been obtained for clinical care reasons). If any of these do not hold, then the case report needs to be reviewed and approved by the IRB.

For any case series or case report (regardless if IRB reviewed or not), every reasonable attempt should be made by the author to contact the patient and/or family or the primary caregiver of the patient so as to inform them of the proposed publication. If applicable, the author must comply with the patient's/family's request not to publish the report OR to present the case in a more de-identifiable manner. HIPAA may still apply to case reports. Please contact the Privacy Office (privacyoffice@nationwidechildrens.org) for guidance and possible patient authorization required.

12. How do I create a consent document?

Use the "TEMPLATE CONSENT DOCUMENT (HRP-502)" to create a consent document. For studies requesting a waiver of documentation of consent, please use HRP-509 - Template - NCH Information Sheet.

Note that 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.

BE SURE TO ALWAYS INCLUDE A VERSION NUMBER/DATE ON YOUR CONSENT DOCUMENTS TO ENSURE THAT YOU USE THE MOST RECENT VERSION APPROVED BY THE IRB. Do not remove the IRB form name and version number when adding your version number to the document. When saving the document, include the version number/date in the title. **(The IRB does not stamp consent forms.)**

Assent should be obtained from subjects ages 9 up to 18 years of age. When relying on an outside IRB and when institutions are relying on the NCH IRB; researchers may follow the policies of the IRB of record or institutional local policies with regard to age of assent. Assent signature is included in the consent template. A separate assent document is available in the eIRB2 library if preferred by the study team but is not required unless specifically requested by the IRB.

See Section, How Do I Document Consent(assent)?

13. Do I need to obtain informed consent in order to screen, recruit, or determine the eligibility of prospective subjects?

The IRB may approve a research proposal in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without the informed consent of the prospective subject or the subject's legally authorized representative, if either of the following conditions are met:

> (1) The investigator will obtain information through oral or written communication with the prospective subject or legally authorized representative, OR

(2) The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

The research protocol should include information about how potential subjects will be identified and recruited in order for the IRB to be able to determine whether informed consent for these activities is required. The protocol templates include an optional HIPAA Waiver section. For those studies including consent of prospective subjects a partial waiver of HIPAA will be required to screen subjects using the medical record and/or clinic schedules before consent is signed.

Contact the IRB Office with additional questions or for further guidance regarding the requirement to obtain HIPAA authorization or a waiver to obtain HIPAA authorization for recruitment purposes.

14. Advertising

1) All recruiting/advertising materials must be reviewed by the IRB.
2) Recruiting/advertising may take the form of physician letters, parent letters, posters, flyers, emails, internet notices, recruitment scripts, television/radio/magazine advertisements, etc.
3) Enough information should be included in the advertising so that prospective participants can readily determine if they are potentially eligible and know where to call for further information. Specifically, recruitment materials are recommended to contain the following:
   - the name and address of the investigator and/or research facility;
   - the condition under study and/or the purpose of the research;
   - in summary form, the criteria that will be used to determine eligibility for the study;
   - a brief list of participation benefits, if any; (compensation is not a benefit of participation)
   - the time or other commitment required of the participants; and
   - the location of the research and the person or office to contact for further information, including phone number or email address.
   - Flyers sent by email or posted for NCH employees must have PI name listed
4) Advertisements should not:
   - state or imply favorable benefits beyond what is outlined in the consent form and protocol.
   - contain exculpatory language.
   - emphasize payment in bold or larger type.
   - contain dollar amounts of compensation. Say instead, phrases like: "You will be compensated for your study participation" or "Reimbursement for your time and travel may be provided". (Avoid phrases like "you will be paid"; "incentive"; "patient")
   - promise "free treatment". Say instead, "study drug will be provided by the sponsor" or "the sponsor will pay for all study costs".
   - be coercive in any way.
5) If the study involves investigational drugs, biologics, or devices, no claims can be made, either explicitly or implicitly:

- inconsistent with FDA labeling;
- that the drug or device is safe or effective for the purposes under investigation; or
- that the drug or device is in any way equivalent or superior to any other drug or device.

6) Terms such as "new drug", "new medication", or "new treatment" are not allowed.
7) Recruitment methods will be reviewed on a case-by-case basis. The IRB will consider sensitivity of the subject matter (e.g. HIV, cancer); risk to subject privacy; and practicality of recruiting methods (i.e. it may not be practical to have the treating physician approach potential subjects).
8) In most cases, recruitment strategies that involve direct subject contact initiated by the PI should involve the treating physician or other professional previously known to the potential participant. This minimizes "cold calling".
9) No recruitment may be conducted until final IRB approval.
10) The Marketing ancillary reviewer box should be checked on all applications that include advertising of any kind.

Types of advertising

1) Recruitment letters:
   - Should state a relationship between the investigator and the family (see #8 above):
     - GI doctor conducting a GI study and wishes to recruit patients seen in the GI clinic says, "I'm conducting a research study on Inflammatory Bowel Disease."
     - Psychologist conducting a GI study and wishes to recruit patients seen in the GI clinic says, "I'm working with the GI doctors on a study of Inflammatory Bowel Disease."
   - Should inform the family that the study team will be contacting the family in the near future.
   - Should include a telephone number and/or email address of the study team for the family to contact for questions, to express interest, or to request no future contact.
2) Recruitment flyers for studies conducted at Nationwide Children's Hospital (NCH) can be displayed or distributed in NCH Clinics only with the permission of the Clinic Directors.
3) Recruitment flyers for studies conducted at external sites (e.g. OSU, other external institutions) can be displayed or distributed in NCH Clinics only with the permission of NCH Leadership and the Clinic Directors and approval by the IRB. Email a copy of the flyer to the IRB Office to IRB@nationwidechildrens.org.
4) Email advertising of a study conducted at NCH intended to be sent to NCH Employees:
   - Text must be approved by the IRB.
   - PI may request an "everyone" email, sent to all NCH employees.
   - Subject to approval by NCH Leadership
   - Flyers sent by email or posted must have PI name listed
5) Email advertising of a study conducted at external sites intended to be sent to NCH employees:
   - If an NCH investigator is listed on the study, see #4 above.
   - If there is no NCH investigator listed on the study, email recruitment is not allowed.
6) Advertising on social media such as Facebook, YouTube, etc., must be approved by the IRB and by NCH Marketing.

7) Recruitment through ResearchMatch.com must be approved by the IRB before submitting to the Program Manager, Center for Clinical & Translational Sciences, for posting.

15. Compensation

1) Compensation for participation:
   - For time and inconvenience.
   - Amount, method and timing of payment should not be coercive.
   - Payment cannot be contingent upon study completion.
   - Bonus payments for study completion not allowed.
   - Should be fully described, including amounts and timing of payments, in consent form.
   - Compensation must be paid to the subject.
   - Compensation is taxable. If total compensation (single study or multiple studies) is greater than $600/year, Research Finance will issue a 1099 form.
   - Assent form should not include dollar amount, only that subject will be paid for participating.
   - For FDA-regulated research, should not include compensation for participation in a trial offered by a sponsor to involve a coupon good for a discount on the purchase price of the product once it has been approved for marketing.
   - Lotteries/raffles as a recruitment method or incentive to participate in research are approved on a case-by-case basis.
2) PI bonus payments are not allowed.

16. Reimbursement

- For expenses incurred while participating, e.g. travel, hotel, parking, meals, etc. Receipts must be submitted to Research Finance.
- Clearly state in the consent form what is paid/reimbursed by the study sponsor and what the participant will be responsible for.
- Reimbursement is not taxable.

17. 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 or review. If you believe your activity may not be Human Research, refer to WORKSHEET: Human Subject Determination (HRP-310) and the "Determination of Research Request Form" located in the Library > General section of the eIRB2 Web site. If you still have questions, contact the IRB Office at IRB@nationwidechildrens.org prior to developing your Investigator Protocol.

- Exempt: Certain types of Human Research may qualify for an exempt category of research. It is the responsibility of the organization, not the investigator, to determine whether Human Research meets the exempt categories. Review the IRB Office'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 (Full) board. Review the IRB Office'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 (Full) IRB: Non-Exempt Human Research that does not qualify for review using the expedited procedure must be reviewed by the convened IRB.

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

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

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

19. How does the IRB decide whether to approve Human Research?

The criteria for IRB approval can be found in the "WORKSHEET: Exemption (HRP-312)" for exempt Human Research and the "WORKSHEET: Criteria for Approval (HRP-314)" for non-

exempt Human Research. The latter worksheet references other checklists that might be relevant. All checklists and worksheets can be found on the eIRB2 Website.

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

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

20. What will happen after IRB review?

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

- If the IRB has approved the Human Research: The Human Research may commence once all other organizational approvals have been met. IRB approval 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, write up your response and submit it to the IRB.
- 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 to the IRB Chair.

21. What are my obligations after IRB approval?

1) Do not start Human Research activities until you have the final IRB approval letter.
2) Do not start Human Research activities until you have obtained all other required institutional approvals, including approvals of departments or divisions that require approval prior to commencing research that involves their resources.
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 application with any changes to the study personnel using the "Team Member Information" activity in the eIRB2 modification Smartform.

An "Other Parts of the Study" modification must be submitted to change PI.

6) Personally conduct or supervise the Human Research. Recognize that the Principal 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?")
      i) Single subject protocol exceptions should be submitted via the modification process.
   b) A continuing review application as requested in the approval letter. (See "How do I submit continuing review?"
   c) A continuing review application when the Human Research is closed. (See "How Do I Close Out a Study?")
8) Respond promptly to clarification or modification requests by the IRB.
   a) Modifications requested are valid for 30 days. Discard submissions and resubmit as new after thirty days.
   b) Clarifications requested are valid for six months. Discard submissions and resubmit as new after six months of inactivity.
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.

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13) Outlined below are the reporting requirements for the IRB.
   a) Note that investigators may have additional reporting obligations as specified by the study sponsor or oversight agency.
   b) For reporting guidelines when relying on an external IRB, please see the section "What are my obligations as an investigator when relying on an external IRB?" number 9.

14) Unless subject to different IRB reporting requirements by a federal agency, investigators must report all local and participating site (if sIRB) Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO) to the IRB within 5 business days of discovery.

Adverse Events that meet the definition of a UPIRTSO should be reported through the RNI Smartform in eIRB2. Please use the following naming conventions for RNI submissions: Subject number/ID; Initial or Update #; Description (e.g. Subject #01 Initial—HIPAA breach or Subjects (100) Initial—HIPAA Breach).

a) UPIRTSOs are Adverse Events determined by the Principal Investigator to be:
   i) Unexpected,
   ii) Related or Possibly Related to the Research Intervention, and
   iii) serious or otherwise suggests that the research places the subject or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

15) Please note that the vast majority of Adverse Events will not meet the definition of an Unanticipated Problem Involving Risk to Subjects or Others (UPIRTSO) and need not be reported to the IRB within the 5-business day window. Expected Adverse Events or Adverse Events which do not meet the three elements in #14 should be reported at continuing review.

16) Local (or participating site) Adverse Events which are fatal or life-threatening, unexpected and related or possibly related to the research intervention must be reported to the IRB **within 24 hours** of learning of the event. (*Note: It is recognized that the information available during this 24-hour period may not be sufficient to permit accurate completion of the RNI Smartform in eIRB2. However, the IRB should, at a minimum, be notified of the fatal or life-threatening adverse event during this time frame, with subsequent follow-up submission of a more detailed written report.*)

Some examples of possible UPIRTSOs might include (list is not all inclusive):
(Items below not meeting the UPIRTSO definition should be reported at the next continuing review)

i) New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor report, or investigator finding) indicates an increase in the frequency or magnitude of a previously known risk, or uncovers a new risk.
ii) An investigator brochure, package insert, or device labeling is revised to indicate an increase in the frequency or magnitude of a previously known risk, or describe a new risk
iii) Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a research protocol

iv) Protocol violation that harmed subjects or others or that indicates subjects or others might be at increased risk of harm
v) Complaint of a subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm
vi) Any changes significantly affecting the conduct of the research
vii) Non-compliance with the federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance.
viii) Audit, inspection, or inquiry by a federal agency and any resulting reports (e.g., FDA Form 483.)
ix) Written reports of DSMBs
x) Failure to follow the protocol due to the action or inaction of the investigator or research staff.
xi) Breach of confidentiality.
xii) Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject.
xiii) Incarceration of a subject in a study not approved by the IRB to involve prisoners.
xiv) Complaint of a subject that cannot be resolved by the research team.
xv) Premature suspension or termination of the protocol by the sponsor, investigator, or institution.
xvi) Unanticipated adverse device effect (any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects).

22. What are my obligations as the overall study PI for an sIRB study?

1) Coordinating with HRPP personnel to determine whether this institution's IRB can act as the single IRB for all or some institutions participating in the study or if an external IRB will assume oversight.
2) Identifying all sites that will be engaged in the human research and requiring oversight by the IRB.
3) Ensure that all sites receive a request to rely on the reviewing IRB and that all institutional requirements are satisfied before a study is activated at a relying site.
4) Collaborate with the reviewing IRB to document roles and responsibilities for communicating and coordinating key information from study teams and the IRB or HRPP at relying sites.
5) Respond to questions or information requests from study teams or the IRB or HRPP staff at relying sites.
6) Provide relying site investigators with the policies of the reviewing IRB.

7) Provide relying site investigators with the IRB-approved versions of all study documents.
8) Preparation and submission of IRB applications on behalf of all sites. This includes initial review, modifications, personnel updates, reportable new information and continuing review information for all sites.
9) Establishing a process for obtaining and collating information from all sites and submitting this information to the reviewing IRB. This includes site-specific variations in study conduct, such as the local consent process and language, subject identification and recruitment processes and local variations in study conduct.
10) Ensuing that consent forms used by relying sites follow the consent template approved by the reviewing IRB and include required language as specified by the relying sites.
11) Providing site investigators with all determinations and communications from the reviewing IRB.
12) Submitting reportable new information from relying sites to the reviewing IRB in accordance with the terms outlined in the authorization agreement or communication plan.
13) Reporting the absence of continuing review information from relying sites if they do not provide the required information prior to submission of the continuing review materials to the reviewing IRB. Notifying the relying site of their lapse in approval and applicable corrective actions.
14) Providing study records to the relying institution, reviewing IRB or regulatory agencies upon request.

23. What are my obligations as investigator when relying on an external IRB?

1) Obtain appropriate approvals from this institution prior to seeking review by another IRB.
2) Comply with determinations and requirements of the reviewing IRB.
3) Provide the reviewing IRB with requested information about local requirements or local research context issues relevant to the IRB's determination prior to IRB review.
4) Notifying the reviewing IRB when local policies that impact IRB review are updated.
5) Cooperating in the reviewing IRB's responsibility for initial and continuing review, record keeping and reporting and providing all information requested by the reviewing IRB in a timely manner.
6) Disclosing conflicts of interest as required by the reviewing IRB and complying with management plans that may result.
7) Promptly reporting to the reviewing IRB any proposed changes to the research and not implementing those changes to the research without prior IRB review and approval, except where necessary to eliminate apparent immediate hazards to the participants.
8) When enrolling participants, obtain, document and maintain records of consent for each participant or each participant's legally authorized representative.
9) Promptly follow all reporting requirements for all local Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO). The definition and examples of UPIRTSOs can be found in "What are my obligations after IRB approval?" numbers 13-16.
    a. Submit an RNI to the reviewing IRB following the reviewing IRB reporting SOPs and policies.

b. Submit an RNI Smartform in eIRB2 to the NCH IRB within 5 business days of discovery for all local Adverse Events that meet the definition of a UPIRTSO. Indicate that an RNI has also been submitted to the reviewing IRB. Please use the following naming conventions for RNI submissions: Subject number/ID; Initial or Update # (if requested) or sIRB determination; Description (e.g. Subject #02 sIRB determination – Protocol Violation).
c. Local Adverse Events which are fatal or life-threatening, unexpected and related or possibly related to the research intervention must be reported to the NCH IRB **within 24 hours** of learning of the event. (*Note: It is recognized that the information available during this 24-hour period may not be sufficient to permit accurate completion of the RNI Smartform in eIRB2. However, the IRB should, at a minimum, be notified of the fatal or life-threatening adverse event during this time frame, with subsequent follow-up submission of a more detailed written report.*)
d. Submit to the NCH IRB a follow-up RNI after the reviewing IRB has made a determination for the submission. Include the reviewing IRB's determination in the submission and reference the original NCH RNI submitted to the NCH IRB.
e. NOTE: Only local Adverse Events should be reported to the NCH IRB. The vast majority of Adverse Events will not meet the definition of an Unanticipated Problem Involving Risk to Subjects or Others (UPIRTSO) and need not be reported to the NCH IRB within the 5-business day window. Expected Adverse Events or Adverse Events which do not meet the definition of UPRIRTSO should be reported following the SOPs and policies of the reviewing IRB (e.g. at continuing review) and will not be submitted to the NCH IRB.

10) Providing the reviewing IRB with data safety monitoring reports in accordance with the reviewing IRB's reporting policy.
11) Reporting non-compliance, participant complaints, protocol deviations or other events according to the requirements specified in the reliance agreement.
12) Specifying the contact person and providing contact information for researchers and research staff to obtain answers to questions, express concerns, and convey suggestions regarding the use of the reviewing IRB.

24. How do I document consent (assent)?

Always use the current IRB-approved consent document. (See TEMPLATE CONSENT DOCUMENT HRP-502.) Complete all items in the signature block, including dates and time.

The following are the requirements for 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 sponsor requires a witness, the witness signs and dates the consent document.
- For subjects who cannot read and whenever required by the IRB or the sponsor, a witness to the oral presentation signs and dates the consent document.
- A copy of the signed and dated consent document is to be provided to the subject.

Short form consent is an alternative to using a translated consent form. The short form may be used for five or fewer limited English proficiency speakers in a particular language for a study. After five subjects are enrolled in a particular language, the entire consent must be translated and approved by the IRB before enrolling any more subjects in that language. The short form document templates and guidance document are available in the eIRB2 library.

The following are the requirements when using the short form consent for limited English proficiency subjects:

- The subject or representative signs and dates the short form consent document.
- The individual obtaining consent signs and dates the English consent document.
- The witness to the oral presentation signs and dates the short form consent document and the English consent document. Note: the witness should be fluent in both English and the other language.
- Copies of the signed and dated consent documents are provided to the person(s) signing those documents.

Short Form Consent in a Multi-Visit or Long-Term Study

- Informed consent is an ongoing process. Therefore, the research team must be able to communicate with the subject for the duration of the study. The research team should arrange for a translator to be available at subsequent visits to ensure that subject has an opportunity to ask questions, understands the responses and receives relevant study information.

- If the study requires multiple visits or the subject's participation will last more than 60 days, a translated version of the complete IRB approved informed consent document should be submitted to the IRB for approval within 30 days of enrollment. The PI/PI Proxy must submit an IRB Modification form with the translated Informed Consent Document and certification of translation. Once the IRB approves translated version the document should be provided to the subject/subject's LAR as soon as possible. Contact the IRB with questions or to propose alternate plans to protect these vulnerable subjects.

25. Assent

Assent should be obtained from subjects ages 9 up to 18 years of age. When relying on an outside IRB and when institutions are relying on the NCH IRB; researchers may follow the policies of the IRB of record or institutional local policies with regard to age of assent. Assent is documented in the consent document. The consent document template has an assent signature line on the signature page. A separate assent document is available in the eIRB2 library if preferred by the study team but is not required unless specifically requested by the IRB.

26. eConsent

Electronic consent is allowed with IRB approval and 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. Subjects must be provided with a copy of the signed consent (signed by both the study team and subject/representative) either by email or paper.

27. Phone consent

Telephone consent is allowed with adequate justification and IRB approval of reading the written consent over the phone or using a phone script. The subject/representative should have a copy of the consent to reference during the conversation. The phone script 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 Office's "WORKSHEET: Criteria for Approval (HRP-314)", to ensure that these elements are addressed. Subjects must be provided with a copy of the signed consent (signed by both the study team and subject/representative) either by email or paper.

NOTE: If your study is not approved for telephone consent but you encounter a situation where it would be a hardship for a subject/representative to sign a written consent, phone consent using the written consent document may be allowed with prior IRB approval. Contact the IRB Office at IRB@nationwidechildrens.org. Document in the subject study file that telephone consent was obtained. Have a witness present on the PI-side to verify consent. Subjects must be provided with a copy of the signed consent either by email or paper.

28. Waiver of documentation of consent

There may be studies where written documentation of consent is not feasible. Often, the research involves no procedures for which written documentation of the consent process is normally required outside of the research context, e.g., surveys. See the IRB Office's "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" for criteria for approval for this type of consent.

29. Waiver or alteration of consent

Minimal risk studies may be conducted with an IRB-approved waiver (or alteration) of the consent process. See the IRB Office's "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" for criteria for approval of a waiver.

30. How do I submit a modification (amendment)?

Complete the Modification SmartForm in the electronic IRB system and attach all requested supplements, have the SmartForm submitted by the PI (or PI Proxy) 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.

Study personnel, other than the PI, can be updated using the "Study Team Member Information" activity in the Modification SmartForm. An "Other Parts of the study" modification must be submitted to change PI. Review the "Submission Checklist" on the homepage of the IRB website by clicking here or searching for "IRB" on Anchor for helpful tips.

31. How do I submit continuing review?

Complete the Continuing Review SmartForm in the electronic IRB system and attach all requested supplements, and have the SmartForm submitted by the PI by clicking the "Submit" activity. Maintain electronic copies of all information submitted to the IRB in case revisions are required. The number of subjects enrolled equals the number of consents signed. NCH IRB considers participants enrolled in a study once the consent form is signed.

If the continuing review application is not received by the date requested in the approval letter, IRB approval will expire and the study is closed. Contact the IRB Office immediately regarding submitting a continuing review application. You (PI) may also be restricted from submitting any new Human Research applications until the completed continuing review application has been received and approved. See IRB SOP: Expiration of IRB Approval (HRP-063).

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 when 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 and provide a written list of the currently enrolled subjects and why they will be harmed by stopping Human Research procedures.

32. How do I close out a study?

Complete the Continuing Review SmartForm in the electronic IRB system and attach all requested supplements, and have the SmartForm 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, you may be restricted from submitting any new Human Research applications until the completed study continuing review application has been received.

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

33. How long do I keep records?

Maintain your Human Research records as described in the study protocol, 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. Records must be stored as described in the IRB-approved protocol (e.g., NCH secure drives, locked cabinets, etc.)

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

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

Contact the IRB Office at IRB@nationwidechildrens.org 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 applicable).

If you fail to submit the report within five days or the IRB application for initial review within 30 days, you may be restricted from submitting any new Human Research until the report and IRB application for initial review (if applicable) 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.

35. 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 eIRB2 Web Site under "Library".

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

IRB Office
700 Children's Drive
Columbus, OH 43205
Email: IRB@nationwidechildrens.org
(614) 722-2708

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

36. HIPAA approval

The IRB serves as the privacy board for research under the guidance of the NCH Privacy Office. All studies are reviewed to ensure that privacy and protected health information (PHI) are properly protected. The protocol (HRP-503 PROTOCOL TEMPLATE or HRP-508 SITE SPECIFIC PROTOCOL SUPPLEMENT or HRP-580 - NCH TEMPLATE SHORT PROTOCOL) requires a discussion of provisions to protect the privacy interests of subjects.

37. CLINICALTRIALS.GOV

NIH-funded clinical trials are required to be posted on ClinicalTrials.gov. For guidance, contact the Research Compliance Office.

Appendix A-1 *Additional Requirements for DHHS-Regulated Research*[2]

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.
5. When research is covered by a certificate of confidentiality, researchers:
    a. May not disclose or provide, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains; or
    b. May not disclose or provide to any other person not connected with the research the name of such an individual or any information, document, or biospecimen that contains identifiable, sensitive information about such an individual and that was created or compiled for purposes of the research.
    c. May disclose information only when:
        i. Required by Federal, State, or local laws (e.g., as required by the Federal Food, Drug, and Cosmetic Act, or state laws requiring the reporting of communicable diseases to State and local health departments), excluding instances of disclosure in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding.

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

ii. Necessary for the medical treatment of the individual to whom the information, document, or biospecimen pertains and made with the consent of such individual;
iii. Made with the consent of the individual to whom the information, document, or biospecimen pertains; or
iv. Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human participants in research.

d. Researchers must inform participants of the protections and limitations of certificates of confidentiality (see language in HRP-502 - TEMPLATE CONSENT DOCUMENT).
   i. For studies that were previously issued a Certificate and notified participants of the protections provided by that Certificate, NIH does not expect participants to be notified that the protections afforded by the Certificate have changed, although IRBs may determine whether it is appropriate to inform participants.
   ii. If part of the study cohort was recruited prior to issuance of the Certificate, but are no longer activity participating in the study, NIH does not expect participants consented prior to the change in authority, or prior to the issuance of a Certificate, to be notified that the protections afforded by the Certificate have changed, or that participants who were previously consented to be re-contacted to be informed of the Certificate, although the IRB may determine whether it is appropriate to inform participants.
e. Researchers conducting research covered by a certificate of confidentiality, even if the research is not federally funded, must ensure that if identifiable, sensitive information is provided to other researchers or organizations, the other researcher or organization must comply with applicable requirements when research is covered by a certificate of confidentiality.

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

1. When a subject withdraws from a study:[3]
    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:[4]
        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.

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

iii. An investigator must not commercially distribute or test market an investigational new drug.

b. Follow FDA requirements for general responsibilities of investigators[5]
   i. An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.
   ii. An investigator must, in accordance with the provisions of 21 CFR §50, obtain the informed consent of each human subject to whom the drug is administered, except as provided in 21 CFR §50.23 or §50.24 of this chapter.
   iii. Additional specific responsibilities of clinical investigators are set forth in this part and in 21 CFR §50 and 21 CFR §56.

c. Follow FDA requirements for control of the investigational drug[6]
   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[7]
   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.

[5] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.60
[6] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.61
[7] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.62

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[8]
   i. Progress reports: The investigator must furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained.
   ii. Safety reports: An investigator must promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator must report the adverse effect immediately.
   iii. Final report: An investigator must provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation.
   iv. Financial disclosure reports:
      1. The clinical investigator must provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under 21 CFR §54.
      2. The clinical investigator must promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

f. Follow FDA requirements for assurance of IRB review[9]
   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[10]
   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.

[8] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.64
[9] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.66
[10] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.68

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[11]

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.[12]

i. An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with 21 CFR §50.

b. Specific responsibilities of investigators[13]

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.

[11] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.69
[12] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.100
[13] http://www.accessdata.fda.gov/SCRIPTs/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.110

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:[14]

i. All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.

ii. Records of receipt, use or disposition of a device that relate to:

1. The type and quantity of the device, the dates of its receipt, and the batch number or code mark.
2. The names of all persons who received, used, or disposed of each device.
3. Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.

iii. Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital charts, and the nurses' notes. Such records must include:

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

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

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

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[15]
   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[16]
   i. Unanticipated adverse device effects. An investigator must submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
   ii. Withdrawal of IRB approval. An investigator must report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
   iii. Progress. An investigator must submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.
   iv. Deviations from the investigational plan:
      1. An investigator must notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency.
      2. Such notice must be given as soon as possible, but in no event later than 5 working days after the emergency occurred.
      3. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the

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

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 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.

c. It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.
d. Although a subject is not obliged to give his/her reasons for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reasons, while fully respecting the subject's rights.

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

accountability at the trial site to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

c. The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product. These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product received from the sponsor.
d. The investigational product should be stored as specified by the sponsor and in accordance with applicable regulatory requirements.
e. The investigator should ensure that the investigational product 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 may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.
   c. Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

d. None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.
e. The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval opinion by the IRB.
f. The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.
g. Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.
h. Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.
i. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.
j. Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:
    i. That the trial involves research.
    ii. The purpose of the trial.
    iii. The trial treatments and the probability for random assignment to each treatment.
    iv. The trial procedures to be followed, including all invasive procedures.

v. The subject's responsibilities.
vi. Those aspects of the trial that are experimental.
vii. The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
viii. The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
ix. The alternative procedures or courses of treatment that may be available to the subject, and their important potential benefits and risks.
x. The compensation and/or treatment available to the subject in the event of trial related injury.
xi. The anticipated prorated payment, if any, to the subject for participating in the trial.
xii. The anticipated expenses, if any, to the subject for participating in the trial.
xiii. That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
xiv. That the monitors, the auditors, the IRB, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
xv. That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
xvi. That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
xvii. The persons to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
xviii. The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
xix. The expected duration of the subject's participation in the trial.
xx. The approximate number of subjects involved in the trial.

k. Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

l. When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

m. Except as described 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, enrollment of the subject should require measures described in the protocol and/or elsewhere, with documented approval opinion by the IRB, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested.

8. Records and Reports

a. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

b. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

c. Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections. Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are

endorsed by the investigator. The investigator should retain records of the changes and corrections.

d. The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirements. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.
e. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.
f. The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.
g. Upon request of the monitor, auditor, IRB, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

9. Progress Reports
    a. The investigator should submit written summaries of the trial status to the IRB annually, or more frequently, if requested by the IRB.
    b. The investigator should promptly provide written reports to the sponsor, the IRB and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.
10. Safety Reporting
    a. All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirements related to the reporting of unexpected serious adverse drug reactions to the regulatory authorities and the IRB.
    b. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.
    c. For reported deaths, the investigator should supply the sponsor and the IRB with any additional requested information (e.g., autopsy reports and terminal medical reports).
    d. Premature Termination or Suspension of a Trial If the trial is prematurely terminated or suspended for any reason, the investigator/institution should

promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirements, should inform the regulatory authorities. In addition:

i. If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB, and should provide the sponsor and the IRB a detailed written explanation of the termination or suspension.
ii. If the sponsor terminates or suspends a trial, the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB and provide the IRB a detailed written explanation of the termination or suspension.
iii. If the IRB terminates or suspends its approval opinion of a trial, the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

11. Final Reports by Investigator: Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the trial's outcome, and the regulatory authorities with any reports required.

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

1. When appropriate, research protocols must be reviewed and approved by the IRB prior to 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. When conducting multi-site research, a formal agreement between organizations is required to specify the roles and responsibilities of each party.
9. 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)."
10. Any unanticipated problems involving risks to subjects or others for any DoD-supported research must be promptly (no longer than within five days) reported to the DoD Office for Human Research Protections.
11. Any suspension or termination of DoD supported research must be promptly (no longer than within five days) reported to the DoD Office for Human Research Protections.

Appendix A-5 *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 "DOE IRB Template for Reviewing Human Subjects Research Protocols that Utilize Personally Identifiable Information (PII)" (http://humansubjects.energy.gov/other-resources/documents/IRB-TemplateForReviewingPIIprotocols2014a.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-6 *Additional Requirements for Department of Justice (DOJ) Research*

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

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

c. A statement that participation is completely voluntary and that the subject may withdraw consent and end participation in the project at any time without penalty or prejudice (the inmate will be returned to regular assignment or activity by staff as soon as practicable).
d. A statement regarding the confidentiality of the research information and exceptions to any guarantees of confidentiality required by federal or state law. For example, an investigator may not guarantee confidentiality when the subject indicates intent to commit future criminal conduct or harm himself or herself or someone else, or, if the subject is an inmate, indicates intent to leave the facility without authorization.
e. A statement that participation in the research project will have no effect on the inmate subject's release date or parole eligibility.

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

1. Each school at which the research is conducted must provide an assurance that they comply with the Family Educational Rights and Privacy Act (FERPA) and the Protection of Pupil Rights Amendment (PPRA).
2. Provide a copy of all surveys and instructional material used in the research. Upon request parents of children[17] involved in the research[18] 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)."

[17] 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.
[18] 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-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)."

Appendix A-9 ***Single IRB Studies***

1. That National Institutes of Health expects that all sites participating in multi-site studies involving non-exempt human subjects research funded by the NIH will use a single Institutional Review Board (sIRB) to conduct the ethical review required by the Department of Health and Human Services regulations for the Protection of Human Subjects at 45 CFR Part 46.
    a. This policy applies to the domestic sites of NIH-funded multi-site studies where each site will conduct the same protocol involving non-exempt human subjects research, whether supported through grants, cooperative agreements, contracts, or the NIH Intramural Research Program. It does not apply to career development, research training or fellowship awards.
    b. This policy applies to domestic awardees and participating domestic sites. Foreign sites participating in NIH-funded, multi-site studies will not be expected to follow this policy.
    c. Exceptions to the NIH policy will be made where review by the proposed sIRB would be prohibited by a federal, tribal, or state law, regulation, or policy. Requests for exceptions that are not based on a legal, regulatory, or policy requirement will be considered if there is a compelling justification for the exception. The NIH will determine whether to grant an exception following an assessment of the need.
2. [Reserved.]

Appendix A-10 *Additional Requirements for Research Subject to EU General Data Protection Regulations (GDPR)*

1. Human Research involving personal data about individuals located in (but not necessarily citizens of) European Union member states, Norway, Iceland, Liechtenstein, and Switzerland is subject to EU General Data Protection Regulations.
2. For all prospective Human Research subject to EU GDPR, contact institutional legal counsel or your institution's Data Protection Officer to ensure that the following elements of the research are consistent with institutional policies and interpretations of EU GDPR:
    a. Any applicable study design elements related to data security measures.
    b. Any applicable procedures related to the rights to access, rectification, and erasure of data.
    c. Procedures related to broad/unspecified future use consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens.
3. Where FDA or DHHS regulations apply in addition to EU GDPR regulations, ensure that procedures related to withdrawal from the research, as well as procedures for managing data and biospecimens associated with the research remain consistent with Appendices A-1 and A-2 above.

Appendix A-11 *Emergency/Disaster Preparedness Considerations for Investigators Conducting Human Research*

Investigators conducting human research should be aware of the following additional considerations associated with managing Human Research during an emergency/disaster scenario (e.g., extreme weather events, natural disasters, man-made disasters, infectious disease pandemics, etc.) related to investigators' ongoing interactions with research subjects and the institutional review board (IRB) in such cases.

During Emergency/Disaster Scenarios: Deciding Whether a Study-Specific Risk Mitigation Plan for Ongoing Research Is Needed

In general, investigators should develop a study-specific emergency/disaster risk mitigation plan for their research unless one of the following is true:

- Research does not involve in-person interaction with research subjects.
- Research can be conducted as written while adhering to additional institution-level and HRPP-level guidance and requirements regarding the emergency/disaster event.
- The research is externally sponsored, and the sponsor has developed a protocol-specific risk mitigation plan for the research.
- The research has been voluntarily placed on hold for recruitment and all research procedures (except for necessary follow-up procedures to be done consistently with additional institution-level and HRPP-level guidance and requirements regarding the emergency/disaster event).

Tools and Resources for Developing Study-Specific Emergency/Disaster Risk Mitigation Plans for Ongoing Research

Review "HRP-108 - FLOWCHART - Study-Specific Emergency-Disaster Risk Mitigation Planning" and "HRP-351 - WORKSHEET - Protocol-Specific Emergency-Disaster Risk Mitigation Plan" for general guidance on developing study-specific risk mitigation plans.

Voluntary Holds on Human Research Activities

Investigators may voluntarily elect to place all recruitment, enrollment and research procedures on temporary hold during emergency/disaster scenarios if doing so will better ensure the safety of research subjects and would not create any additional risks to the safety and welfare of research subjects. Such voluntary holds on research activity do not require IRB notification or review.

Submitting Study-Specific Emergency/Disaster Risk Mitigation Plans for IRB Review

If immediate modification of the research is necessary to eliminate an apparent immediate hazard to a subject, take action and notify the IRB within five business days following the standard pathway to submit reportable new information.

For all other study modifications made to ensure the ongoing safety of research subjects during emergency/disaster scenarios, submit a study amendment and all relevant new or modified study materials to the IRB.

Other Reportable New Information Considerations During Emergency/ Disaster Scenarios

The IRB's list of reportable events includes two items for which additional clarification and guidance may be helpful during emergency/disaster scenarios:

- ***"Failure to follow the protocol due to the action or inaction of the investigator or research staff."*** Emphasis on action or inaction of the investigator or research staff has been added because this requirement does not include action or inaction of the research subject. For example, study teams may notice an increase in the number of subjects who do not arrive for scheduled research visits under emergency/disaster circumstances. Failure of a research participant to appear for a scheduled research visit is not noncompliance due to action or inaction by the investigator or research staff, and therefore does not require reporting to the IRB.
- ***"Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject."*** During emergency/disaster scenarios, there will be cases where there is sufficient time to receive IRB approval of any proposed modifications to previously approved research, and in such cases, investigators should follow standard IRB procedures for submitting modifications. However, there will be other cases where investigators must make more immediate changes to the protocol or investigational plan to minimize or eliminate immediate hazards or to protect the life and well-being of research participants. Such changes may be implemented without IRB approval, but are required to be reported to the IRB within five business days afterward in accordance with IRB policies and procedures for submitting reportable new information.

APPENDIX B

DETERMINATION OF HUMAN SUBJECT RESEARCH vs QI

PURPOSE: To have an understanding when projects are research and when they require IRB review.

DEFINITIONS (for additional definitions, see Policy IRB-001):

Research:
DHHS definition: A **systematic investigation**, including research development, testing and evaluation, designed to develop or contribute to **generalizable knowledge**.

FDA definition: Any experiment that involves an FDA-regulated test article and one or more **human subjects** and is already subject to FDA requirements. [21 CFR 56.102(c)]

Systematic Investigation:
- Attempt to answer research questions (e.g. hypothesis)
- Collects data or information in an organized and consistent way
- Data or information is analyzed in some way
- Conclusions are drawn from the results

Generalizable Knowledge:
- Knowledge contributes to a theoretical framework of an established body of knowledge
- Results are expected to be generalized to a larger population beyond the site of data collection or population studied
- Results are intended to be replicated in other settings

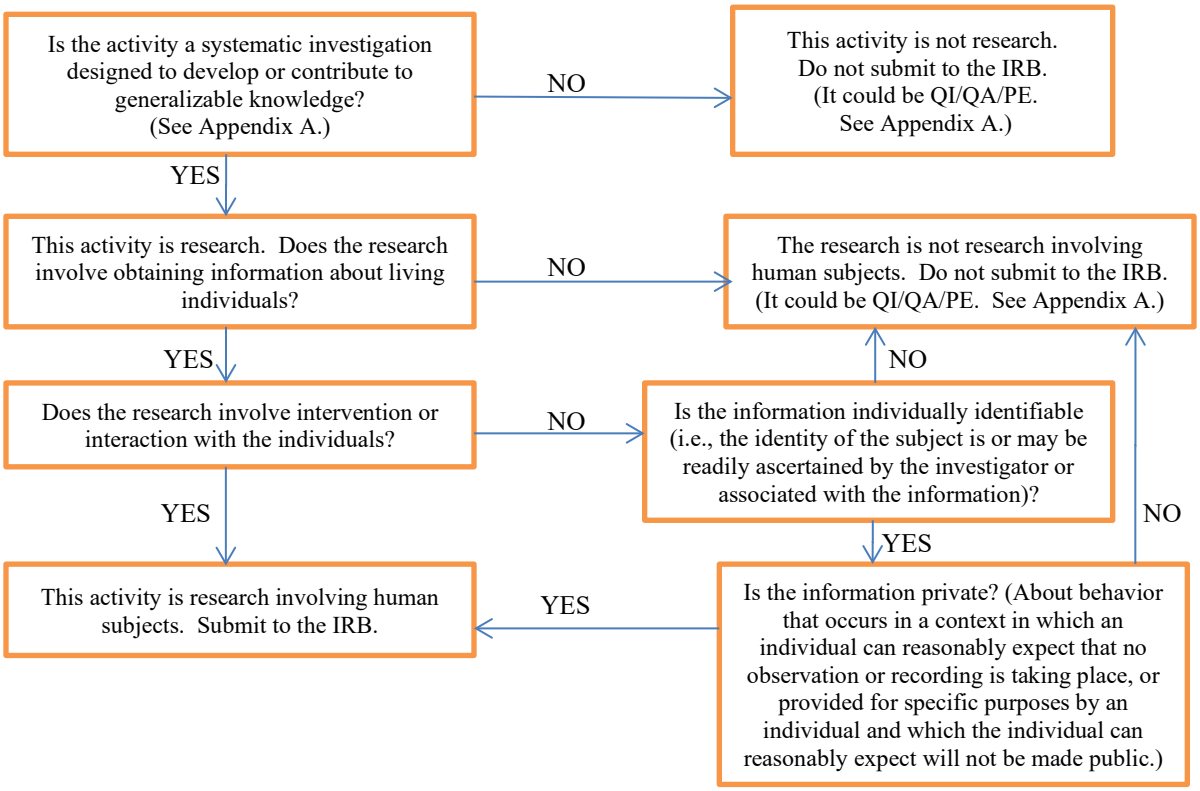
Human Subject:
DHHS definition: A living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through **intervention** or **interaction** with the individual, or (2) identifiable private information. [45 CFR 46.102(f)]

FDA definition: An individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. FDA, 21 CFR 50.3(g), 21 CFR 56.102(e). A human subject includes an individual on whose specimen a medical device is used. [21 CFR 812.3(p)]

Intervention:
Includes both physical procedures by which data are gathered and manipulations of the subject or the subject's environment that are performed for research purposes. [45 CFR 46.102(f)]

Interaction:
Includes communication or interpersonal contact between investigator and subject. [45 CFR 46.102(f)]

Investigators should use the following decision tree and table to decide if their project is (1) research; (2) human subjects research; or (3) Quality Improvement (QI), Quality Assurance (QA), or Program Evaluation (PE). If unsure, contact the IRB Office for guidance.



APPENDIX A

	Research	QI/QA	Program Evaluation
Purpose	• To answer a question or test a hypothesis • To establish clinical practice standards where none are already accepted. • Testing new interventions that are beyond current science and experience, such as new treatments. Involves care practices, interventions, or treatments that are not standard (neither consensus-based nor evidence-based, not in existence). • Testing an experimental drug/device/biologic. • Intent is to contribute to generalizable knowledge (can be replicated elsewhere) AND is designed in such a way (e.g. randomization of subjects; case vs. control) that the findings will be generalizable.	• To assess or improve a process/program/system OR to improve performance as judged by established/ accepted standards (existing knowledge), evidence-based or consensus-based. • May or may not be generalizable outside the institution. • The clinical practice unit (hospital, clinic, division, or center) agrees that this is a QI/QA project that is being implemented to improve process or delivery of care. (May be mandated as part of operations.)	• Improve a specific program. • Activity mandated by program as part of its operations.
Design	To answer a question or test a hypothesis.	To improve performance.	Provide feedback to program to improve that program
Findings	Findings are not expected to directly affect institutional or programmatic practice.	Findings are expected to directly affect institutional practice and may identify needed corrective actions.	Findings are expected to directly affect conduct of program and identify improvements.
Population	Usually involves a subset of individuals. A statistical justification for sample size may be used to ensure endpoints are met.	Includes all or most receiving a particular treatment or process.	Information on all or most participants within or affected by receiving a particular treatment or undergoing a particular practice or process.
Benefits	• Knowledge sought may or may not benefit current subjects, but may benefit future patients. • Conducting this project may contribute to professional benefit (tenure, obtaining grants, research career path).	• Knowledge sought directly benefits a process/program/ system. • Participants expected to benefit directly from activities. • Project is conducted regardless of any professional benefit.	No benefit to participants expected; evaluation concentrates on program improvements or whether the program should continue.

Risks/Burdens	May put subjects at risk.	• Does not increase risk to patients, with exception of possible privacy/ • confidentiality concerns. • Does not over-ride clinical decisions.	
Funding	• Funding from an external organization (federal, industry) based on support of a "research paradigm" to carry out the proposed activity. • May receive internal "research-designated" funding.	Internal funding, if any.	Internal funding, if any.
Publishing	• Intent to publish in order to contribute to generalizable knowledge. • Publishing may contribute to professional benefit (tenure, obtaining grants, research career path).	Intent to publish/present in order to share learning is appropriate but does not require IRB review as long as the publication refers to the activity as QI/QA, not research.	Program evaluations are not generally published.

Examples of QA/QI Activities NOT Considered Research:

- Evidence-based approach to reducing pharmacy prescription errors.
- Standardizing care of patients presenting to the ED with asthma exacerbation using the evidence-based guideline published by the The American Academy of Pediatrics.
- Any QI/QA initiative, and presentation/publication of results, that are conducted within NCH only and serve to measure or improve NCH's ability to meet or exceed an existing national standard of care or benchmark (e.g. JACHO).
- Submission of data to a national or state registry/database that is mandated at the state or federal level with the primary purpose of improving the delivery of clinical care.
- Submission of data to a national or state registry/database that directly impacts reimbursements and funding available from the State, Department of Health, or Federal Centers for Medicare & Medicaid Services (CMS) based on performance and/or clinical or quality outcomes.

Examples of QA/QI Activities that ARE Considered Research (Combined) and must be submitted to the IRB:

- Any QA initiative designed to develop a standard of care or benchmark.
- Any activity that proposes comparisons of one or more prospective interventions that are deliberately administered or made available (through a randomization or other process) to some patients or providers and not to others.

NOTE:

1. Determination can be made by the Principal Investigator or a designated member of the IRB. If a PI is in doubt, they should contact the IRB Office.
2. The criteria in this policy should be used to make the determination.
3. Determinations made by the IRB will be communicated by an eIRB2 review letter (see SOP, Full Review) or by email if no submission to IRB has been made.
4. Projects determined not to be human subjects research are still subject to HIPAA requirements.

5. If a journal asks for an IRB review, the IRB Office will provide this policy.

Revision History:
5/15/18: added sIRB and GDPR language
12/10/18: added ClinicalTrials.gov; revised advertising; added Research vs QI guidance
12/26/18: revised financial conflict section per K. Dunn comments