NCH HRPP: Protecting Research Participants, Advancing Knowledge

Investigator Manual[1]

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Owners: M. Brackeen; H. Granville; H. Phillips
Approver: D. Durbin

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NOTE: All referenced "HRP" documents can be found in the elRB2 Library.

1. Scope

Throughout this document "organization" refers to Nationwide Children's Hospital, Inc. and all 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: Section 5, "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 "HRP-907 Determination of Research Request Form", located in Library > General section of the eIRB2 Website. 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 Human Subject Research Determination Request be submitted through a New Study application (SmartForm) in eIRB2 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 must 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.

a. The mission of the Human Research Protection Program.

b. The ethical principles that the organization follows governing the conduct of Human Research.

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c. The applicable laws that govern Human Research.

d. When the organization becomes “engaged in Human Research” and when someone is acting as an agent of the organization conducting Human Research.

e. The types of Human Research that may not be conducted.

f. The roles and responsibilities of individuals within the organization.

5. What trainings do 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?” and/or the Education/Training page on IRB ANCHOR).

All research personnel at NCH are required to complete the “Responsible Conduct of Research” CITI course. Investigators and staff conducting research involving no more than minimal risk to subjects must complete the online CITI “Human Subjects Protection” course (*Can choose to take Biomedical and/or Social & Behavioral). Investigators and staff conducting research on studies involving consenting 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 human subjects protection courses.

- The CITI site can be accessed at http://www.citiprogram.org/.
- Training is valid for a three-year period (except for the “Responsible Conduct of Research” that is valid for four years) 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 and be listed on the eIRB2 Study Team Member section. 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. It is the Principal Investigator's responsibility to ensure that all members of the study team complete the required training based on the research being conducted and complete the refresher courses before they expire.
- See Training Tracker for other optional human research training courses.

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6. *What financial interests do my staff and I need to disclose to 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?*

a. Complete the New Study SmartForm in the electronic IRB system and attach all requested supplements.

   i. BE SURE TO CHECK ALL APPLICABLE ANCILLARY REVIEWERS. See "Manage Ancillary Reviewers" link in the left column. Review HRP-309-WORKSHEET - Ancillary Review Matrix (eIRB2 > Library > "Worksheets" tab) to determine which ancillaries are appropriate for your study.

b. The PI (and/or other study team members) may be requested by the reviewer to have a copy of the PI's Curriculum Vitae (CV) or NIH Biosketch attached as a document in the "other" section of the eIRB2 submission (this includes new study submission and submissions involving the change of a PI).

c. 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:

   ii. Satisfy Conflict of Interest Disclosure requirements (all engaged research staff).

   iii. Satisfy all required training (all engaged research staff).

   iv. 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.

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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?*

If you believe your activity may not be Human Research, refer to HRP-310 - WORKSHEET - Human Research Determination (eIRB2 > Library > "Worksheets" tab) and the "HRP-907-Determination of Research Request Form" (eIRB2 > Library > "General" tab). **The IRB cannot provide determination after a project has already begun.** If you still have questions, contact the IRB Office at IRB@nationwidechildrens.org prior to developing your Investigator Protocol.

A sponsor provided protocol can be submitted with your New Study SmartForm along with the "HRP-508 - Template - Site Supplement to Sponsor Protocol" form.

If you do not have a protocol, use the protocol templates available in the eIRB2 Library > Templates tab 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:

a. The bullet points in the protocol templates serve as guidance to investigators when developing an Investigator Protocol for submission to the IRB.

b. 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.

c. 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.

d. 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 applicable. Do <u>not</u> simply enter N/A and do not delete sections of the protocol template.

e. 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.

    i. Adults unable to provide legally effective consent

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ii. Individuals who are not yet adults (infants, children, teenagers)

iii. Pregnant women

iv. Prisoners

f. If you are conducting community-based participatory research, you may contact the IRB Office for information about:

i. Research studies using a community-based participatory research design

ii. Use of community advisory boards

iii. Use of participant advocates

iv. Partnerships with community-based organizations

g. If you are conducting planned emergency research, you may review HRP-047-SOP Planned Emergency Research for the procedure on conducting this type of research.

11. How do I access HIPAA data for preparation to research?

Activities considered "preparatory to research" under HIPAA (45 CFR §164.512(i)) allow researchers to review PHI to prepare for a research study. However, these activities must be limited to what is necessary for designing the study or assessing feasibility (e.g., determining if enough records exist to answer a research question). Preparatory activities are limited to actions needed to design the study, such as:

- Determining feasibility (e.g., checking the availability of records or data points).
- Estimating sample size.
- Developing inclusion/exclusion criteria.

The preparatory to research provisions under HIPAA (45 CFR §164.512(i)) are strictly for activities necessary to prepare for research. These activities allow access to PHI but do not permit recording, retaining, or using that data for research purposes, including analysis. Data accessed during this phase are meant only to inform study design, not to contribute directly to the research findings.

While data from the preparatory to research phase can support identifying potential participants, you **must** have IRB approval to move forward with recruitment.

When preparing a preparatory to research request, please use the following form: HRP-904 - HIPAA PREPARATION FOR RESEARCH REQUEST FORM (eIRB2 > Library > “Templates” tab). A completed form can be sent to the IRB via email, IRB@nationwidechildrens.org and will be reviewed, signed, and returned to you.

12. *What about a case study or case series?*

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

For a case report (five or less 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 contribution of cases to a larger case series outside of NCH contact the IRB (IRB@nationwidechildrens.org) for guidance.

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.

13. *How do I create a consent document?*

Use the "HRP-502 - NCH INFORMED CONSENT TEMPLATE" 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 "HRP-314 - Worksheet - Criteria for Approval" 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, you may want to include the version number/date in the file name to ensure proper record keeping. **The IRB does not issue expiration dates on consent forms (i.e., stamping consent forms).**

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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 regarding 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.

(For more information on documenting consent (assent), please see Section 25, “How Do I Document Consent(assent)?”)

14. Do I need to obtain informed consent 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 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 authorization** 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 partial waiver of HIPAA authorization for recruitment purposes.

15. Advertising/Recruitment

1) All recruitment/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:

- that are 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) It is permissible for current research subjects to receive payments for identifying or referring potential study participants. This payment cannot be contingent on whether or not the potential participant enrolls in or finishes the study. The discussion should be limited to telling the person about the study and seeing if they would be interested in obtaining additional information from the study team. There must be no undue influence, and if the person is not interested, the discussion should be terminated. The number of referrals each participant can provide may be limited by the IRB during review.

9) 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".

10) No recruitment may be conducted until final IRB approval.

11) The Marketing (Research Advertising) ancillary reviewer should be checked on all applications that include advertising of any kind. Additionally, complete the "Marketing Form for Study Recruitment" (eIRB2 > Library > "Templates" tab) and add the form to the study submission form on Local Site Documents question #2 Recruitment Materials.

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."
- Inform the family that the study team will be contacting the family in the near future.
- 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 the Clinic Director and approval by the IRB. Submit the external flyer along with an HRP-907 Determination of Research Request Form as a New Study in eIRB2.

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, see #3 above.
6) Advertising on social media such as Facebook, YouTube, etc., must be approved by the IRB and by NCH Marketing. Research teams may not use their own personal social media accounts to advertise for research.
7) Recruitment through ResearchMatch.com must be approved by the IRB before submitting to the Program Manager, Center for Clinical & Translational Sciences, for posting.

16. Compensation

1) Compensation for participation:
   - For time and inconvenience
   - Amount, method and timing of payment should not represent undue influence or 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 for achieving recruitment goals or meeting specific benchmarks related to recruitment or enrollment are not allowed.

17. Reimbursement

- For expenses incurred while participating, (e.g. travel, hotel, parking, meals, etc.). Receipts may need to 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.

18. 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 "HRP-310 - WORKSHEET - Human Research Determination" and the "HRP-907 Determination of Research Request Form" located in the Library > General section of the eIRB2 Web site. **The IRB cannot provide determination after a project has already begun**. 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 "HRP-312 - Worksheet - Exemption Determination" 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 "HRP-313 - Worksheet - Expedited Review" 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.

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19. 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.
- 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.

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

The criteria for IRB approval can be found in the "HRP-312 - Worksheet - Exemption Determination" for exempt Human Research and the "HRP-314 - Worksheet - Criteria for Approval" 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 can be 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.

21. 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

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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.

22. 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 appropriate study source documents have been created to accurately document study procedures. A list of recommended documents can be found in "HRP-430 - CHECKLIST - Investigator Quality Improvement Assessment" found in the eIRB2 library. Refer for each study type entitled "Regulatory Documentation for Each Study"
5) 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.
6) Update the application with any changes to the study personnel using the "Study Team Member Information" activity in the eIRB2 modification Smartform.
    a) Note: When needing to change the PI, submit an "Other Parts of the Study" modification type. See Section #32, "How do I change the study Principal Investigator?" for more information.

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7) 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.
8) Submit to the IRB (when applicable):
    a) Proposed modifications as described in this manual. (See Section 31, “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 Section 33, “How do I submit continuing review?”)
    c) A Check-in form for minimal risk studies as requested in the approval letter. (See Section 34, “How do I submit a Check-in Form?”)
    d) A continuing review application when the Human Research is closed. (See Section 35, “How do I close out a study?”)
9) Respond promptly to clarification or modification requests by the IRB.
    a) Modifications requested are valid for sixty (60) days. Discard submissions and resubmit as new after sixty (60) days.
    b) Clarifications requested are valid for three (3) months. Discard submissions and resubmit as new after three (3) months of inactivity.
10) 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.
11) Do not provide payments to professionals in exchange for referrals of potential subjects (“finder’s fees.”)
12) Do not accept payments designed to accelerate recruitment that were tied to the rate or timing of enrollment (“bonus payments”).
13) Ensure study data does not originate from Care Everywhere unless pulled into the NCH

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patient chart for clinical reasons before research use.

14) Reporting of all deviations from the protocol at the study yearly continuing review or the biennial check-in process. If deviations create a situation that rises to the level of adverse event, report as directed below.

    See additional requirements of various federal agencies in Appendix A. These represent additional requirements and do not override the baseline requirements of this section.

Reporting Adverse Events to the IRB

1) 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 Section 24, "What are my obligations as an investigator when relying on an external IRB?" number 9.
2) 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. The IRB recommends the following naming convention 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.
3) 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 as described by the IRB approved protocol or at continuing review.
4) 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*

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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.)

5) Investigators should include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

    a) a detailed description of the adverse event, incident, experience, or outcome;

    b) an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents a UPRITSO; and

    c) a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

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

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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).

23. 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

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initial review, modifications, personnel updates, reportable new information and continuing review information, or Check-in 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) Ensuring 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.
15) More information can be found concerning sIRB on the IRB Anchor site in the sIRB-Reliance Studies area.

24. 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 Section 22, "What are my obligations after IRB approval?" subsection *Reporting Adverse Events*.

    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. The IRB recommends the use of 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.

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11) Reporting to the reviewing IRB non-compliance, participant complaints, protocol deviations or other events according to the requirements specified in the reliance agreement. All local protocol deviations should be reported to the NCH IRB when submitting annual continuing review approval documents from the reviewing IRB.

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.

13) More information can be found concerning external IRB studies on the IRB Anchor site in the sIRB-Reliance Studies area.

25. How do I document consent (assent)?

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

The following are the requirements for consent documents:

a. The subject or representative signs and dates the consent document.

b. The child-subject signs and dates the assent section of the consent document. (if applicable, see Section 26 “Assent” for more information.)

c. The individual obtaining consent signs and dates the consent document.

d. Whenever the IRB or sponsor requires a witness, the witness signs and dates the consent document.

e. 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.

f. For studies involving sexually transmitted infection and/or mental health research or treatment, minors may consent without parental permission from 14 up to 17 years.

g. A copy of the signed and dated consent document is to be provided to the subject.

When subjects speaking a non-English language (e.g., Spanish) are expected to enroll in a study, the entire consent form should be translated and approved by the IRB during the study approval process. For instance, if a subject is coming from another country to participate in a study, the consent form for the study should be translated prior to their arrival.

Short form consent is an alternative to using a translated consent form when limited English proficiency subjects are unexpectedly encountered. 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:

1. The subject or representative signs and dates the short form consent document.
2. The child-subject signs and dates the assent section of the short form consent document. (if applicable, see Section 26 “Assent” for more information.) If no assent section is available on the short form, the assent of the child subject may be sought verbally and that assent documented in the study file.
3. The individual obtaining consent signs and dates the English consent document.
4. 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.
5. Copies of all the signed and dated consent documents are provided to the subject or representative.

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 short form consenting is used and 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 subject or representative should be reconsented at next study interaction. Contact the IRB with questions or to propose alternate plans to protect these vulnerable subjects.

Translated Consent Documents

- Signatures on fully translated consent documents:
    - The subject or representative signs and dates the translated consent document.
    - The child-subject signs and dates the assent section of the translated consent document. (if applicable, see Section 26 “Assent” for more information.)
    - The individual obtaining consent signs and dates and English version of the consent document.

- The witness to the oral presentation signs and dates both the English and Translated consent documents. Note: the witness should be fluent in both English and the other language.
- Copy of both the consent documents are provided to the subject or representative.

- Certification of Translation for Translated Consent Documents
  - While there is no specific regulatory mandate for translator qualifications, 45 CFR §46.116 requires that information provided to participants be understandable. This implies the need for translators who are fluent in both languages and familiar with the content.
    - *Best Practice:*
      - Use certified translators (e.g., accredited by the American Translators Association) for important documents.
    - *Good Practice:*
      - Have translations undergo a second independent review or back-translation process for accuracy.
  - If professional certification is unavailable, bilingual study staff may translate materials if at least one of the following conditions are met:
    - They are fluent in both languages
    - They are competent in the subject matter being translated.

26. Assent

Documented 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.

27. 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 "HRP-314 - Worksheet - Criteria for Approval" 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.

Studies with drugs/devices/biologics that are overseen by the FDA may only use specific software programs for eConsent which comply with FDA 21 CFR Part 11 requirements.

28. 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 "HRP-314 - Worksheet - Criteria for Approval", 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.

29. 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 "HRP-411 - Checklist - Waiver of Written Documentation of Consent" for criteria for approval for this type of consent.

30. 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 "HRP-410 - Checklist - Waiver or Alteration of Consent Process" for criteria for approval of a waiver.

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

Complete the Modification SmartForm in the electronic eIRB2 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 “Modification Checklist” on the homepage of the IRB website by clicking here or searching for “IRB” on Anchor for helpful tips.

- The PI (and/or other study team members) may be requested by the reviewer to have a copy of the PI’s Curriculum Vitae (CV) or NIH Biosketch attached as a document in the “other” section of the eIRB2 submission (this includes new study submission and submissions involving the change of a PI).

32. How do I change the study Principal Investigator?

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

Modifications changing PI

The new PI assuming responsibility for the study must have appropriate education, training, and experience to take responsibility for the study. Studies changing PI may be required to bring the study up to code by using the most current study documents in the eIRB2 library. Contact the IRB at IRB@nationwidechildrens.org with questions.

All modifications that are changing PI must include:

- A letter or email from the incoming PI confirming they will take responsibility for the specific study.
- All study documents with PI name updated with the new PI name with the exception of consent forms if the study has concluded enrollment.
- A plan to reconsent or notify study participants of new PI
- Please note: the reviewer may request the Curriculum vitae (CV) or NIH Biosketch for the incoming PI be uploaded with the submission form (Local Site Documents > #3 Other attachments).

Procedures for Offboarding and Leave of Absence

Principal Investigators leaving the institution permanently will be instructed to have a PI Proxy assigned in the eIRB2 system before they depart the institution. This can be done by the current PI without IRB submission by clicking “assign PI Proxy” on the main study page in eIRB2.

• To continue study procedures until another PI can assume responsibility for the study, the IRB Chair, Vice Chairs, HRPP Director, or IRB Manager must add a comment to the main study in eIRB2 verifying that the PI proxy is qualified (e.g., including but not limited to appropriate training, education, expertise, credentials, protocol requirements and, when relevant, privileges) to perform procedures and duties of the PI for the study.

• The PI Proxy can perform as study PI for up to 60 calendar days from the original PI departure date and study procedures can continue. A modification assigning a new PI to the study should be submitted by day 30 and approved by the IRB before the 60 day period is complete or the IRB may administratively close the study.

• If no PI Proxy is assigned as of the PI's departure date or if the PI Proxy is found to be unqualified, all study procedures must stop (unless required to ensure subject safety). A modification assigning a new PI to the study should be submitted within 30 days of PI's departure or the IRB may administratively close the study

• Principal Investigators on leave exceeding 30 days should have a PI proxy assigned in eIRB2 (chosen by them) who is qualified (e.g., including but not limited to appropriate training, education, expertise, credentials, protocol requirements and, when relevant, privileges) to perform procedures and duties of the PI for the study.

33. 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 for studies involving consent. NCH IRB considers participants enrolled in a study once the consent form is signed.

1. NCH IRB Guidance for Total Number of Subjects Enrolled for Retrospective Studies
    - When **accessing** a chart for a retrospective chart review with a full HIPAA and consent waiver, the subject **is** considered 'enrolled.'
        a. Review and collect data of subjects meeting inclusion/exclusion criteria to be used for research analysis. (e.g., in an enrollment log)
        b. If the subject reviewed does not meet the requirements for the study, they are still considered enrolled because the chart was **accessed** under a full HIPAA waiver.
        c. This subject identifier *does* need to be recorded (e.g., in a screening log) and all data needs to be kept for at least 6 years after study closure. Identifiers should be destroyed as outlined in the protocol HIPAA waiver request.

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    d. Document enrollment including the total number from both logs (screening + enrollment) when reporting in a CR study closure or check-in form.
- When accessing a chart for research screening (for recruitment purposes only) with a partial HIPAA Waiver these individuals are considered “screened” and not “enrolled”.
    a. This screening information does not need to be reported at continuing review or check in.
    b. This subject identifier ***does*** need to be recorded (e.g., in a screening log) and kept for at least 6 years after study closure.
    c. Identifiers should be destroyed as outlined in the protocol HIPAA waiver request.

If the continuing review application is not received by the date requested in the approval letter, IRB approval will expire and the study will enter into a “lapsed” state. 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 and federal law.

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.

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 HRP-063 - SOP - Expiration of IRB Approval (eIRB2 > Library > “Standard Operating Procedures” tab).

34. How do I submit a Check-in Form?

The PI and Primary Contact for studies determined to be either be minimal risk (expedited) or exempt will receive an email with a link to complete the Check-In form. Studies will receive a notice which have been opened for two or more years and will receive it the month before the study was approved (ex. a study approved in June will be sent a notification in May). If the Check-In is not completed within one (1) month, a reminder will be sent. The link to the Check-In system can also be found on the IRB ANCHOR page.

Responses to the Check-In form must reflect the current status of the study. Once a

Check-In is completed, a report will be generated and uploaded into eIRB2. If the form determines additional action is required (i.e. submitting a study closure or a modification), PI and/or study staff must do so within 15 business days of the completed Check- In.

If a Check-In has not been completed or the additional action has not been addressed at 6 months, the PI may be placed on restricted status due to noncompliance.

35. 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 the continuing review form 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 form is received.

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 form has been received.

36. 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.) Subject identifiers should be destroyed in the time period described in the study protocol and eIRB2 submission form(s).

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

37. 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 and/or the Office of Research Regulatory Affairs (ORRA) ORRATEAM@nationwidechildren.org immediately to discuss the situation. If there is no time to make this contact, see the "HRP-322 - WORKSHEET - Emergency Use" for the regulatory criteria allowing such a use and make sure these are followed. Use the "HRP-506 - TEMPLATE CONSENT DOCUMENT - Emergency or Compassionate Device Use" 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.

38. 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:

Institutional Review Board Office

575 Children's Crossroad

Columbus, OH 43215

IRB@nationwidechildrens.org

IRB.Reliance@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 "HRP-101 - HUMAN RESEARCH PROTECTION PROGRAM PLAN" under "Reporting and Management of Concerns."

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39. 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 NCH IRB protocol templates require a discussion of provisions to protect the privacy interests of subjects.

40. CLINICALTRIALS.GOV

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

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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:

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

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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.

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.

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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

[3] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126489.pdf
[4] eCFR :: 21 CFR 312.7 -- Promotion of investigational drugs.

findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

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

b. Follow FDA requirements for general responsibilities of investigators[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.

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[5] eCFR :: 21 CFR 312.60 -- General responsibilities of investigators.
[6] eCFR :: 21 CFR 312.61 -- Control of the investigational drug.
[7] eCFR :: 21 CFR 312.62 -- Investigator recordkeeping and record retention.

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ii. Case histories.

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

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

e. Follow FDA requirements for investigator reports[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.

[8] eCFR :: 21 CFR 312.64 -- Investigator reports.

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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.

   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

[9] eCFR :: 21 CFR 312.66 -- Assurance of IRB review.
[10] eCFR :: 21 CFR 312.68 -- Inspection of investigator's records and reports.
[11] eCFR :: 21 CFR 312.69 -- Handling of controlled substances.
[12] eCFR :: 21 CFR 812.100 -- General responsibilities of investigators.

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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.

      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:

[13] eCFR :: 21 CFR 812.110 -- Specific responsibilities of investigators.
[14] eCFR :: 21 CFR 812.140 -- Records.

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

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

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

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

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

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

[15] eCFR :: 21 CFR 812.145 -- Inspections.

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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 plan or the rights, safety, or welfare of human subjects, FDA and IRB also is required.

[16] eCFR :: 21 CFR 812.150 -- Reports.

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

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

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

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

1. 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 (GCP) and the applicable regulatory requirements. The rights, safety and well-being of the participants are the most important considerations and should prevail over interests of science and society.
2. Clinical trials should be scientifically sound for their intended purpose and based on adequate and current scientific knowledge and approaches.
    a. The available nonclinical and clinical information on an investigational product(s) should be adequate to support the proposed clinical trial.
    b. Clinical trials should be scientifically sound and reflect the state of knowledge and experience with the investigational product(s), including, if applicable, the condition being treated, diagnosed or prevented; the current understanding of the underlying biological mechanism (of both the condition and the investigational product); and the population for which the investigational product is intended.
    c. There should be periodic review of current scientific knowledge and approaches to determine whether modifications to the trial are needed, since new or unanticipated information may arise once the trial has begun.
3. Investigator's Qualifications and Training
    a. 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.
    b. The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and/or in other information sources provided by the sponsor.
4. Resources
    a. The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of eligible participants within the recruitment period as agreed with the sponsor.
    b. The investigator should have sufficient time, an adequate number of available and qualified staff, and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
5. Responsibilities
    a. The investigator may delegate trial-specific activities to other persons or parties. The investigator may be supported by the sponsor in the identification of a suitable service provider(s); however, the investigator retains the final decision on whether the service provider intended to support the investigator is appropriate based on information provided to the sponsor. The investigator retains the ultimate responsibility and should maintain appropriate oversight of the persons or parties undertaking the activities delegated to ensure the rights,

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safety and well-being of the trial participants and reliability of the data. The level of investigator oversight of the delegated activities should depend on the nature of the delegated activities and be proportionate to the importance of the data being protected and the risks to trial participant safety and data reliability.

b. The investigator should ensure that all persons or parties to whom the investigator has delegated trial-related activities are appropriately qualified and are adequately informed about the relevant aspects of the protocol, the investigational product(s), and their assigned trial activities (including activities conducted by staff provided by other parties in accordance with local regulatory requirements). Trial-related training to persons assisting in the trial should correspond to what is necessary to enable them to fulfill their delegated trial activities that go beyond their usual training and experience.
c. The investigator should ensure a record is maintained of the persons and parties to whom the investigator has delegated trial-related activities. Documentation of delegation should be proportionate to the significance of the trial-related activities. In situations where the activities are performed as part of clinical practice, delegation documentation may not be required.
d. Agreements made by the investigator/institution with service providers for trial-related activities should de documented.
e. The investigator/institution should permit monitoring and auditing by the sponsor, inspection by the appropriate regulatory authority(ies) and, in accordance with applicable regulatory requirements, review by IRB(s).

6. Communication with IRB
    a. Submission to the IRB may be made by the investigator/institution or sponsor in accordance with applicable regulatory requirements.
    b. Before initiating a trial, the investigator/institution should have a documented and dated approval from the IRB for the trial protocol, informed consent materials, participant recruitment procedures (e.g., advertisements), and any other trial-related information to be provided to participants.
    c. As part of the investigator's/institution’s or sponsor’s (in accordance with applicable regulatory requirements) submission to the IRB, a current copy of the Investigator's Brochure or basic product information brochure should be provided. If the Investigator's Brochure or basic product information brochure is updated during the trial, the IRB should receive the current version in accordance with applicable regulatory requirements.
    d. As the trial progresses, the investigator/institution or sponsor should provide any updates to the participant information to the IRB in accordance with applicable regulatory requirements.
    e. The investigator or sponsor should submit documented summaries of the trial status to the IRB in accordance with local regulatory requirements or upon request.

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    f. The investigator or the sponsor should promptly communicate to the IRB and where applicable, to the institution any changes significantly affecting the conduct of the trial and/or increasing risk to participants.
7. Compliance with Protocol
    a. The investigator/institution should sign the protocol, or an alternative contract, to confirm agreement with the sponsor.
    b. The investigator/institution should comply with the protocol, GCP and applicable regulatory requirements.
    c. The investigator should document all protocol deviations. In addition to those identified by the investigator themselves, protocol deviations related to their trial participants and their conduct of the trial may be communicated to them by the sponsor. In either case, the investigator should review the deviations, and for those deviations deemed important, the investigator should explain the deviation and implement appropriate measures to prevent a recurrence, when applicable.
    d. The investigator should follow the protocol and deviate only where necessary to eliminate an immediate hazard(s) to trial participants. In case of deviations undertaken to eliminate immediate hazard to trial participants, the investigator should inform the sponsor promptly.
    e. The investigator should report information on the immediate hazard, the implemented change and the subsequent proposed protocol amendment, if any, to the IRB and, where applicable, regulatory authorities.
8. Premature Termination or Suspension of a Trial
    a. If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial participants and should assure appropriate therapy and follow-up for the participants.
    b. Where the investigator terminates or suspends their involvement in a trial without prior agreement by the sponsors, the investigator should promptly inform the institution, where applicable, the sponsor, the IRB, and the regulatory authorities in accordance with applicable regulatory requirements and should provide a detailed explanation of the reasons.
    c. If the sponsor terminates or suspends a trial, the investigator/institution, or the sponsor, in accordance with applicable regulatory requirement(s), should promptly inform the IRB and the regulatory authorities and should provide an appropriate explanation.
    d. If the IRB terminates or suspends its approval of a trial, the investigator should inform the institution, where applicable, and the investigator/institution should promptly notify the sponsor.
9. Participant Medical Care and Safety Reporting
    a. Medical Care of Trial Participants
        i. A qualified physician or, where appropriate, a qualified dentist (or other qualified healthcare professionals in accordance with local regulatory

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requirements) who is an investigator or a sub-investigator for the trial, should have the responsibility for trial-related medical care and decisions.

ii. Other appropriately qualified healthcare professionals may be involved in the medical care of trial participants, in line with their normal activities and in accordance with local regulatory requirements.

iii. During and following participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a participant when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

iv. The investigator should inform the participant's primary physician about the participant's involvement in the trial if the participant has a primary physician and agrees to the primary physician being informed.

b. Safety Reporting

i. Adverse events and/or abnormal test results required for safety evaluations (as outlined in the protocol) should be reported to the sponsor according to the reporting requirements and within the time periods specific in the protocol. Unfavorable medical events occurring in participants before investigational product administration (e.g., during screening) should be considered and reported to the sponsor if required by the protocol.

ii. All serious adverse events (SAEs) should be reported immediately (after the investigator reasonably becomes aware of the event) to the sponsor. The investigator should also include an assessment of causality. In accordance with applicable regulatory requirements, the protocol may identify SAEs not requiring immediate reporting, for example, deaths or other events that are endpoints. Subsequent information should be submitted as a follow-up report, as necessary.

iii. For reported deaths, the investigator should supply the sponsor, the IRB and, where applicable, the regulatory authority with any additional requested information (e.g., autopsy reports and terminal medical reports) when they become available.

iv. The investigator may delegate activities for safety reporting to qualified investigator site staff but retains the overall responsibility for safety of participants under their responsibility and compliance with the reporting requirements.

10. Informed Consent of Trial Participants

a. In obtaining and documenting informed consent (paper or electronic format), 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

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Declaration of Helsinki. The informed consent process should include the following:

i. Prior to consenting and enrolling participants, the investigator should have the IRB's documented approval of the informed consent materials and process;
ii. The information should be as clear and concise as possible, use simple language and avoid unnecessary volume and complexity. This is to ensure that the trial participants or their legally acceptable representatives have an adequate understanding of the objectives of the trial, alternative treatments, potential benefits and risks, burdens, their rights, and what is expected of the participants to be able to make an informed decision as to their participant in the trial.
iii. Varied approaches (e.g., text, images, videos and other interactive methods), may be used in the informed consent process including for providing information to the participant. The characteristics of the potential trial population (e.g., participants may lack familiarity with computerized systems) and the suitability of the method of obtaining consent should be taken into consideration when developing the informed consent materials and process. When computerized systems are used to obtain informed consent, trial participants may be given the option to use a paper-based approach as an alternative.
iv. Obtaining consent remotely may be considered where appropriate.
v. Whether the informed consent process takes place in person or remotely, the investigator should assure themselves of the identity of the participant (or legally acceptable representative) in accordance with applicable regulatory requirements.

b. The participant or the participant's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue trial participation. The communication of this information and confirmation of the willingness to continue trial participation should be documented. New information that could impact a participant's willingness to continue participation should be assessed to determine if re-consent is needed (e.g., depending on the stage of the trial, consideration should be given to whether the new information is relevant only to new participants or to existing participants). If re-consent is needed (e.g., information on emerging safety concerns), new information should be clearly identified in the revised informed consent materials. Revised informed consent materials should receive the IRB's approval in advance of use.
c. Neither the investigator, nor the investigator site staff, should coerce or unduly influence a participant to participate or to continue their participation in a trial.
d. None of the information provided to the participant or the participant's legally acceptable representative during the informed consent process, should contain

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any language that causes the participant 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 service providers from liability for negligence.

e. The informed consent process should be conducted by the investigator or other investigator site staff delegated by the investigator, in accordance with applicable regulatory requirements. If the participant is unable to provide consent themselves (e.g., minors, patients with severely impaired decision making capacity), the participant's legally acceptable representative should provide their consent on behalf of the participant.
f. The information provided during the informed consent process and translations should be relevant, clear, simple, concise and understandable to the participant or the participant's legally acceptable representative and the impartial witness, where applicable.
g. Before informed consent may be obtained, the investigator, or investigator site staff delegated by the investigator, in accordance with the protocol and conditions of IRB approvals, should provide the participant or the participant's legally acceptable representative ample time unless justified (e.g., in an emergency situation) and opportunity to inquire about trial details and to decide whether or not to participate in the trial. Questions about the trial should be answered to the satisfaction of the participant or the participant's legally acceptable representative.
h. Prior to trial participation, the informed consent form should be signed and dated by the participant or by the participant's legally acceptable representative, where appropriate, by an impartial witness and by the investigator or delegated investigator site staff who conducted the informed consent discussion. By signing the consent form, the investigator or delegated investigator site staff attests that the informed consent was freely given by the participant or the participant's legally acceptable representative and the consent information was accurately explained to and apparently understood by the participant or the participant's legally acceptable representative. The informed consent process may involve a physical or an electronic signature and date.
i. In emergency situations, when prior consent of the participant is not possible, the consent of the participant's legally acceptable representative, if present, should be requested. When prior consent of the participant is not possible and the participant's legally acceptable representative is not possible and the participant's legally acceptable representative is not available, enrollment of the participant should require measures described in the protocol and/or elsewhere, with documented approval by the IRB, to protect the participant's rights, safety and well-being and to ensure compliance with applicable regulatory requirements. The participant or the participant's legally acceptable representative should be informed about the trial as soon as possible, and consent as appropriate should be requested.

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j. If a participant or the legally acceptable representative is unable to read, an impartial witness should be present (remotely or in-person) during the entire informed consent discussion. After the informed consent form and any other information is read and explained to the participant or the participant's legally acceptable representative, and they have orally consented to the participant's trial participation, and if capable of doing so, have signed and dated the informed consent form, the witness should sign and date the consent form. By signing the consent form, the witness attests that the consent information was accurately explained to, and apparently understood by, the participant or the participant's legally acceptable representative, and that informed consent was freely given by the participant or the participant's legally acceptable representative.

k. The informed consent discussion and the informed consent materials to be provided to participant should explain the following as applicable:
    i. The purpose of the trial;
    ii. That the trial involves research and summary of the experimental aspects of the trial;
    iii. The trial's investigational product(s) and the probability for random assignment to the investigational product, if applicable;
    iv. The trial procedures to be followed, including all invasive procedures;
    v. What is expected of the participants;
    vi. The reasonably foreseeable risks or inconveniences to the participant and, when applicable, the participant's partner, to an embryo, fetus, or nursing infant;
    vii. The reasonably expected benefits. When there is no intended clinical benefit to the participant, the participant should be made aware of this;
    viii. The alternative procedure(s) or course(s) of treatment that may be available to the participant, and their important potential benefits and risks;
    ix. The compensation and/or treatment available to the participant in the event of trial related injury;
    x. Any anticipated prorated compensation to the participant for trial participation;
    xi. Any anticipated expenses to the participant for trial participation;
    xii. That the participant's trial participation is voluntary, and the participant may decide to stop taking the investigational product or withdraw from the trial, at any time, without penalty or loss of benefits to which the participant is otherwise entitled;
    xiii. The follow-up procedure for participants who stopped taking the investigational product, withdrew from the trial or were discontinued from the trial;

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xiv. The process by which the participant's data will be handled, including in the event of the withdrawal or discontinuation of participation in accordance with applicable regulatory requirements;
xv. That by agreeing to participant in the trial, the participant or their legally acceptable representative allows direct access to source records, based on the understanding that the confidentiality of the participant's medical record will be safeguarded. This access is limited for the purpose of reviewing trial activities and/or reviewing or verifying data and records by the regulatory authority(ies) and the sponsor's representatives, for example, monitor(s) or auditor(s), and in accordance with applicable regulatory requirements, IRB;
xvi. That records identifying the participant will be kept confidential and, to the extent permitted by the applicable regulatory requirements, will not be made publicly available. If the results of the trial are published, the participant's identity will remain confidential. The trial may be registered on publicly accessible and recognized databases, per applicable regulatory requirements;
xvii. That the participant or the participant's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue trial participation;
xviii. The person(s) to contact for further trial information and the trial participant's rights, and whom to contact in the event of suspected trial-related injury;
xix. The foreseeable circumstances and/or reasons under which the participant's trial participation may be terminated.
xx. The expected duration of the participant's trial participation;
xxi. The approximate number of participants involved in the trial;
xxii. That trial results and information on the participant's actual treatment, if appropriate, will be made available to them should they desire it when this information is available from the sponsor.

l. Prior to participation, the participant or the participant's legally acceptable representative should receive a copy (paper or electronic) of the signed informed consent form and any other informed consent materials provided, in accordance with applicable regulatory requirements. During trial participation, the participant or the participant's legally acceptable representative should receive a copy of the consent form updates and any other updated informed consent materials provided.
m. When a minor is to be included as a participant, age-appropriate assent information should be provided and discussed with the minor as part of the consent process, and assent from the minor to enroll in the trial should be obtained as appropriate. As process for re-consent should be considered if,

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during the course of the trial, the minor reaches the age of legal consent, in accordance with applicable regulatory requirements.

n. When a clinical trial includes participant who may only be enrolled in the trial with the consent of the participant's legally acceptable representative, the participants should be informed about the trial in a manner that facilitates their understanding and, if capable, the participant should sign and date the informed consent form or assent form as appropriate.

11. End of Participation in a Clinical Trial
    a. When a participant decides to stop treatment with the investigational product, stop trial visits or completely withdraw from a trial; is discontinued from the trial; or reaches the routine end of the trial, the investigator should follow the protocol and other sponsor instructions to determine appropriate follow-up measures. This may include instructions to avoid unnecessary loss of already collected critical data in accordance with applicable regulatory requirements.
    b. Although a participant is not obliged to provide a reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the participant's rights. The investigator should consider if a discussion with the participant or the participant's legally acceptable representative is appropriate. This discussion should focus on the reasons for withdrawal to determine if there are ways to address the concerns such that the participant could reconsider withdrawal without unduly influencing the participant's decision. The investigator or delegated investigator site staff should consider explaining to the participant the value of continuing their participation to minimize trial participants withdrawal. In this process, the investigator should ensure that it does not interfere with the participant's decision to refuse or withdraw participation at any time.
    c. Where relevant, the investigator should inform the participant about the trial results and treatment received when this information is available from the sponsor after unblinding, with due respect to the participant's preference to be informed.
12. Investigational Product Management
    a. Responsibility for investigational product(s), including accountability, handling, dispensing, administration and return, rests with the investigator/institution. The sponsor may facilitate aspects of investigational product management (e.g., by providing forms and technical solutions, such as computerized systems, and arranging distribution of investigational product to trial participants).
    b. When the investigator/institution delegates some or all of their activities for investigational product(s) management to a pharmacist or another individual in accordance with local regulatory requirements, the delegated individual should be under the oversight of the investigator/institution.
    c. Where the investigator has delegated activities related to investigational product management or aspects of these activities have been facilitated by the sponsor,

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the level of investigator oversight will depend on a number of factors, including the characteristics of the investigational product, route and complexity of administration, level of existing knowledge about the investigational product's safety and marketing status.

d. The investigator/institution and/or pharmacist or other appropriate individual, should maintain records of the product's delivery, the inventory, the use by each participant (including documenting that the participants were provided the doses specified by the protocol), and the return to the sponsor and destruction or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial participants. For authorized medicinal products, alternative approaches to the aforementioned may be considered, in accordance with local regulatory requirements.
e. The investigational product(s) should be stored as specified by the sponsor and in accordance with applicable regulatory requirement(s).
f. The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.
g. When applicable, the investigator or a person designated by the investigator/institution should explain the correct use of the investigational product(s) to each participant and should check, at intervals appropriate for the trial, that each participant is following the instructions properly.
h. The investigational product may be shipped to the participant's location or supplied to/dispensed at a location closer to the participant (e.g., at a local pharmacy or local healthcare center). The investigational product may be administered at the participant's location by investigator site staff, the participant themselves, or a caregiver or a healthcare professional.
i. Investigational product management should be arranged and conducted in accordance with applicable regulatory requirements, and safeguards should be in place to ensure product integrity, product use per protocol and participant safety.

13. Randomization Procedures and Unblinding
    a. The investigator should follow the trial's randomization procedures, if any, and in the case of an investigator-blinded trial, should ensure that the treatment randomization code is broken only in accordance with the protocol. In the case of an emergency, to protect participant safety, the investigator should be prepared and capable from the start of the trial to perform unblinding without undue delay and hinderance. The investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, emergency unblinding to protect trial participant, unblinding due to an SAE) of the investigational product(s).
14. Records
    a. In generating, recording and reporting trial data, the investigator should ensure the integrity of data under their responsibility, irrespective of the media used.

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b. The investigator/institution should maintain adequate source records that include pertinent observations on each of the trial participants under their responsibility. Source records should be attributable, legible, contemporaneous, original, accurate and complete. Changes to source records should be traceable, should not obscure the original entry and should be explained if necessary (via an audit trail). The investigator should define what is considered to be a source record(s), the methods of data capture and their location prior to starting the trial and should update this definition when needed. Unnecessary transcription steps in between the source record and the data acquisition tool should be avoided.
c. The investigator should be provided with timely access to data by the sponsor and be responsible for the timely review of data, including relevant data from external sources that can have an impact on, for example, participant eligibility, treatment or safety (e.g., central laboratory data, centrally read imaging data, other institution's records and, if appropriate, electronic patient-reported outcome (ePRO) data. The protocol may provide exceptions for access, for instance, to protect blinding.
d. The investigator should ensure that data acquisition tools and other systems deployed by the sponsor are used as specified in the protocol or trial-related instructions.
e. The investigator should ensure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the data acquisition tools completed by the investigator site (e.g., case report form (CRF)) and in any other required reports (e.g., SAE reports). The investigator should review and endorse the reported data at important milestones agreed upon with the sponsor (e.g., interim analysis).
f. Data reported to the sponsor should be consistent with the source records or the discrepancies explained. Changes or corrections in the reported data should be traceable, should be explained (if necessary) and should not obscure the original entry.
g. The investigator/institution should implement appropriate measures to protect the privacy and confidentiality of personal information or trial participants in accordance with applicable regulatory requirements on personal data protection.
h. Data reported to the sponsor should be identified by an unambiguous participant code that can be tracked back to the identity of the participant by the investigator/institution.
i. For systems deployed by the investigator/institution that maintain and retain trial data/information, the investigator/institution should ensure that such data are protected from unauthorized access, disclosure, dissemination or alteration and from inappropriate destruction or accidental loss.
j. When using computerized systems in a clinical trial, the investigator/institution should do the following:

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i. For systems deployed by the investigator/institution, ensure that appropriate individuals have secure and attributable access;
ii. For systems deployed by the sponsor, notify the sponsor when access permissions need to be changed or revoked from an individual;
iii. For system deployed by the investigator/institution specifically for the purposes of clinical trials, ensure the requirements for computerized systems in section 4 of ICH GCP Annex 1[17] are addressed proportionate to the risks to participants and to the importance of the data;
iv. Where equipment for data acquisition is provided to trial participants by the investigator, ensure that traceability is maintained and participants are provided with appropriate training;
v. Ensure that incidents in the use and operation of computerized systems, which in the investigator/institution's judgment may have a significant and/or persistent impact on the trial data or system security, are reported to the sponsor and, where applicable, to the IRB.

k. The investigator/institution should maintain the trial records as specified in Appendix C of ICH GCP Annex 1 and as required by the applicable regulatory requirement(s). The investigator/institution should have control of all essential records generated by the investigator/institution before and during the conduct of the trial.
l. The investigator/institution should retain the essential records for the required retention period in accordance with applicable regulatory requirements or until the sponsor informs the investigator/institution that these records are no longer needed, whichever is the longest. The investigator/institution should take measures to ensure availability, accessibility and readability and to prevent unauthorized access and accidental or premature destruction of these records.
m. The investigator/institution should keep the sponsor informed of the name of the person responsible for maintaining the essential records during the retention period; for example, when the investigator site closes or an investigator leaves the site.
n. Upon request of the monitor, auditor, IRB, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

15. Reports
    a. 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, if applicable, the regulatory authorities with any required reports.

[17] https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106.pdf

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. Civilian researchers attempting to access military volunteers should seek collaboration with a military researcher familiar with service-specific requirements.
3. 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.
4. 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.
5. Components of the Department of Defense might have stricter requirements for research-related injury than the DHHS regulations.
6. There may be specific educational requirements or certification required.
7. When assessing whether to support or collaborate with this institution for research involving human subjects, the Department of Defense may evaluate this institution's education and training policies to ensure the personnel are qualified to perform the research.
8. When research involves U.S. military personnel, policies and procedures require limitations on dual compensation:
    a. Prohibit an individual from receiving pay of compensation for research during duty hours.
    b. An individual may be compensated for research if the participant is involved in the research when not on duty.
    c. Federal employees while on duty and non-Federal persons may be compensated for blood draws for research up to $50 for each blood draw.
    d. Non-Federal persons may be compensated for research participating other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research.
9. Surveys performed on DOD personnel must be submitted, reviewed, and approved by the DOD Information Management Control Officer (IMCO) after the research protocol is reviewed and approved by the IRB. When a survey crosses DOD components,

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additional review is required. Consult the Department of Defense funding component to coordinate this review.

10. When research involves large scale genomic data (LSGD) collected on DOD-affiliated personnel, additional protections are required:
    a. Additional administrative, technical, and physical safeguards to prevent disclosure of DoD-affiliated personnel's genomic data commensurate with risk (including secondary use or sharing of de-identified data or specimens)
    b. Research will apply an HHS Certificate of Confidentiality
    c. DoD Component security review
11. Data or information sent to a DOD component under a pledge of confidentiality for exclusively statistical purposes must be used exclusively for statistical purposes and may not be disclosed in identifiable form for any other purpose, except with the informed consent of the respondent.
12. When conducting multi-site research, a formal agreement between institutions is required to specify the roles and responsibilities of each party.
13. The following must be reported to the applicable DOD Component Office of Human Research Protections within 30 days:
    a. When significant changes to the research protocol are approved by the IRB or EC:
        i. Changes to key investigators or institutions.
        ii. Decreased benefit or increased risk to participants in greater than minimal risk research.
        iii. Addition of vulnerable populations as participants.
        iv. Addition of DOD-affiliated personnel as participants.
        v. Change of reviewing IRB.
    b. When the organization is notified by any federal body, state agency, official governing body of a Native American or Alaskan native tribe, other entity, or foreign government that any part of an HRPP is under investigation for cause involving a DOD-supported research protocol.
    c. Any problems involving risks to participants or others, suspension or termination of IRB approval, or any serious or continuing noncompliance pertaining to DOD-supported human participant research.
    d. The results of the IRB's continuing review, if required.
    e. Change in status when a previously enrolled participant becomes pregnant, or when the researcher learns that a previously enrolled participant is pregnant, and

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the protocol was not reviewed and approved by the IRB in accordance with 45 CFR 46, Subpart B.

f. Change in status when a previously enrolled participant becomes a prisoner, and the protocol was not reviewed and approved by the IRB in accordance with 32 CFR 219, Subpart C.

g. Closure of a DOD-supported study.

14. For human participant research that would not otherwise be approved but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates, written approval from the DOD Office for Human Research Protections must be obtained through the DOD Component Office of Human Research Protections prior to research starting.

15. 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 HRP-318 - WORKSHEET - Additional Federal Agency Criteria.

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

(See DOE Order 443.1C, Chg 1)

1. Research that involves one or more of the following must be submitted to the appropriate IRB for human subjects research (HSR)/not HSR review and determination:
    a. Study of humans in a systematically modified environment. These studies include but are not limited to intentional modification of the human environment:
        i. Study of human environments that use tracer chemicals, particles or other materials to characterize airflow.
        ii. Study in occupied homes or offices that:
            1. Manipulate the environment to achieve research aims.
            2. Test new materials.
            3. 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.
    b. Use of social media data and/or other publicly available data about individuals or publicly available biospecimens, even if the data or biospecimens appear(s) to be de-identified. *Note: DOE follows the Health Insurance Portability and Accountability Act (HIPAA) and guidance issued by the National Institutes of Standards and Technology, as a minimum, in determining identifiability*.
    c. Human Terrain Mapping (HTM), which is managed as HSR. HTM must be strictly limited to only those projects involving the analysis and modeling of de-identified data.
2. Ensure that final HSR/not HSR determinations for studies that may constitute HSR, including exempt HSR determinations, are made through the appropriate IRB and/or IRB office. For sites that use one or both Central DOE IRB(s) as their IRB(s) of record, the Central DOE office is the responsible office and coordinates with the site HSR leads, as appropriate, to discuss project specific information and convey study determinations.
3. If you submit studies to DOE central or DOE site IRBs, complete additional DOE-specific training that includes a module on recognizing and addressing bias in the design, review and conduct of Human Research.
4. Personally identifiable information (PII) collected and/or used during HSR projects must be protected in accordance with the requirements of DOE Order 206.1, *Department of Energy Privacy Program*, current version. The Central DOE IRBs require submission of DOE's HRP- 490-CHECKLIST-Reviewing Protocols that use Personally Identifiable Information (PII) if your research includes PII. Contact the CDOE at CDOEIRB@orau.org to obtain a copy.

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5. The following must be reported in writing to the DOE human subjects research Program Manager (and, when a National Nuclear Security Administration (NNSA) element is involved, the NNSA HSP Program Manager), even for HSR that meets the regulatory definition of exempt HRS as outlined in 10 Code of Federal Regulations (CFR) Part 745.104.
    a. Prior to initiation of the HSR portion of a new project, involving:
        i. An institution without an established Institutional Review Board (IRB);
        ii. A foreign country;
        iii. The potential for significant controversy (e.g., negative press or reaction from stakeholder or oversight groups);
        iv. Research subjects in a protected class (including the populations identified in Subparts B, C, and D of 45 CFR Part 46), as well as other such as individuals with impaired decision-making capability, or DOE/NNSA Federal or DOE/NNSA contractor employees as human subjects, who may be more vulnerable to coercion and undue influence to participate) that is outside of the reviewing IRB's typical range/scope; or
        v. The generation or use of classified information.
    b. Immediately upon a finding of a suspected or confirmed data breach involving PII in printed or electronic form, report to the IRB, the DOE/NNSA HSP Program Manager(s), and the Integrated Joint Cybersecurity Coordination Center (iJC3), in accordance with the requirements of DOE O 206.1. The appropriate HSP Program Manager must also be notified of any corrective actions taken and consulted regarding the plan for any remaining corrective actions.
    c. Immediately upon learning of a serious adverse event, report to the IRB and the DOE/NNSA HSP Program Manager(s). The appropriate HSP Program Manager must also be notified of any corrective actions taken and consulted regarding the plan for any remaining corrective actions.
    d. The IRB must be notified immediately and the DOE HSP Program Manager (and, when an NNSA element is involved, the NNSA HSP Program Manager) must be notified within two (2) business days of learning of the following and consulted regarding planned corrective actions if any of the following occur:
        i. Unanticipated problems, significant adverse events, and complaints about the research.
        ii. Any suspension or termination of IRB approval of research.
        iii. Any known or potential incidents of non-compliance with requirements of DOE Order 443.1C, Chg.1, 10 CFR Part 745, or 45 CFR Part 46.
6. Requirements for human participant protections for classified research apply to all classified research conducted or supported by the DOE and its national laboratories, including contracts, and including Human Terrain Mapping research.

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7. Researchers conducting human subjects research in any other country or on citizens or other individuals residing in that country must be cognizant of country-specific human subjects research requirements and consult the IRB regarding applicability of such requirements.
8. No human subjects research conducted with DOE funding, at DOE institutions (regardless of funding source)[18], or by DOE or DOE contractor personnel (regardless of funding source or location conducted), whether done domestically or in an international environment, including classified and proprietary research, may be initiated without both a Federalwide Assurance (FWA) or comparable assurance (e.g., Department of Defense assurance) of compliance and approval by the cognizant Institutional Review Board (IRB) in accordance with 10 CFR §745.103.
9. Human subjects research involving multiple DOE sites (e.g., members of the research team from more than one DOE site and/or data or human subjects from more than one DOE site) must be reviewed and approved by one of the Central DOE IRBs prior to initiation, or if authorized by the DOE and/or NNSA HSP Program Manager, other appropriate IRB of record. In all cases, an IRB Authorization Agreement (IAA) or Memorandum of Understanding (MOU) must be in place between the organization(s) conducting the HSR and the organization responsible for IRB review.
10. Human subjects research that involves targeted inclusion of DOE Federal and/or contractor employees or their data must first be reviewed and approved by the appropriate DOE IRB (the DOE site IRB or one of the Central DOE IRBs), or if deemed more fitting by the Federally assured DOE site or Headquarters, other appropriate IRB of record, in accordance with an IAA or MOU negotiated between the DOE site or Headquarters and the organization responsible for IRB review.
11. Classified and unclassified intelligence and intelligence-related HSR regardless of the funding source (including, but not limited to, Strategic Intelligence Partnership Program (SIPP) funded studies, DOE Office of Intelligence and Counterintelligence (DOE-IN) funded studies, and/or studies funded by other DOE program offices that use intelligence datasets), must be reviewed and approved by the Central DOE IRB-Classified.
12. If applicable, federally funded HSR must comply with the requirements of the Paperwork Reduction Act.

[18] HSR conducted by researchers from outside institutions at/using DOE/NNSA user facility capabilities may only be initiated if the researchers have provided documentation of study-specific approval or exemption determination from the IRB/ethics board used by their institution.
If the outside institutions using DOE facility capabilities are not funded by DOE, partnering with any DOE or DOE contractor organization, or using DOE or DOE contractor employees or employee data, their studies will not be expected to comply with all other requirements in this order unless the DOE/NNSA site responsible for the user facility requires such compliance.

13. If applicable, HSR involving visiting student researchers, researchers, and scholars from other countries as members of research teams must comply with Department of State requirements, e.g., those outlined in 22 CFR Part 62, *Exchange Visitor Program*, and *U.S. Department of State Guidance Directive 2024-01*, current version.
14. Equitable payment of human subjects participating in HSR is allowable.
15. Other specific requirements of the DOE research can be found in the “Additional Requirements for Department of Energy (DOE) Research” section in the IRB’s HRP-318 - WORKSHEET - Additional Federal Agency Criteria.

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

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

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

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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.

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c. Significance of anticipated results and their contribution to the advancement of knowledge.

d. Specific resources required from the Bureau of Prisons.

e. Description of all possible risks, discomforts, and benefits to individual subjects or a class of subjects, and a discussion of the likelihood that the risks and discomforts will actually occur.

f. Description of steps taken to minimize any risks.

g. Description of physical or administrative procedures to be followed to: Ensure the security of any individually identifiable data that are being collected for the study.

h. Destroy research records or remove individual identifiers from those records when the research has been completed.

i. Description of any anticipated effects of the research study on institutional programs and operations.

j. Relevant research materials such as vitae, endorsements, sample consent statements, questionnaires, and interview schedules.

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 HRP-318 - WORKSHEET - Additional Federal Agency Criteria.

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.
    a. At least once a year, the researcher shall provide the Chief, Office of Research and Evaluation, with a report of the progress of the research.
    b. At least 12 working days before any report of findings is to be released, the researcher shall 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. The researcher shall include an abstract in the report of findings.
    c. In any publication of results, the researcher shall acknowledge the Bureau's participation in the research project.
    d. The research shall expressly disclaim approval or endorsement of the published material as an expression of the policies or views of the Bureau.
    e. Prior to submitting for publication the results of a research project conducted under this subpart, the researcher shall provide two copies of the material, for informational purposes only, to the Chief, Office of Research and Evaluation, Central Office, Bureau of Prisons
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 HRP-318 - WORKSHEET - Additional Federal Agency Criteria.

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

1. Each school at which the research is conducted must provide an assurance that they comply with the Family Educational Rights and Privacy Act (FERPA) and the Protection of Pupil Rights Amendment (PPRA).
2. Provide a copy of all surveys and instructional material used in the research. Upon request parents of children[19] involved in the research[20] 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 HRP-318 - WORKSHEET - Additional Federal Agency Criteria.

[19] 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.
[20] Research or experimentation program or project means any program or project in any research that is designed to explore or develop new or unproven teaching methods or techniques.

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

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

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

1. The 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. The Office for Human Research Protections expects that all sites located in the United States participating in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States. The reviewing IRB will be identified by the Federal department or agency supporting or conducting the research or proposed by the lead institution subject to the acceptance of the Federal department or agency supporting the research.

    The following research is not subject to this provision:

    a. Cooperative research for which more than single IRB review is required by law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe); or

    b. Research for which any Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context.

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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.

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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 Planning" 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.

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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.

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