



Research Security & Integrity

UNIVERSITY OF COLORADO **BOULDER**

INSTITUTIONAL REVIEW BOARD

Investigator Manual

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IRB Contact Information

If you have questions about your role and responsibilities after reading this document, please contact the IRB at irbadmin@colorado.edu or (303) 735-3702.

Purpose of this Manual

This document is designed to guide you through your responsibilities related to the conduct of Human Research that are specific to the University of Colorado Boulder.

General information regarding Human Research protections and relevant federal regulations and guidance is incorporated into the required human research protections training. For additional information see below: “Required Training for Investigators and Stud Staff”

Human Research

Research that requires IRB oversight must meet the Department of Health & Human Services definition of “Research” and “Human Subject” as defined in [45 CFR 46.102](#):

“Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.”

“Human Subject means a living individual about whom an investigator (whether professional or student) conducting research:

Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or

Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.”

A survey for determining whether an activity is Human Research can be found on the IRB’s website: [IRB Decision Tool](#). Use this survey for guidance, keeping in mind that the IRB is the final arbiter as to whether an activity constitutes Human Research requiring IRB oversight.

It is your responsibility to obtain IRB review and approval before conducting Human Research. If you are uncertain, or have questions, about whether an activity is Human Research, contact the IRB Office who will provide you with a determination. Only written determinations from the IRB are official. If you wish to have a written determination, submit an Initial Application submission via the Electronic Research Administration system (eRA).

Human Research Protection Program

A Human Research Protection Program (HRPP) is an organization-wide system to protect human subjects in research. As an Investigator, you share a critical responsibility with the IRB and Institutional Official to uphold the principles of human subjects research and protect the rights and welfare of all subjects. To learn more about your role in the HRPP, see “POLICY: Human Research Protection Program (HRP-010).”

Principal Investigator Eligibility Requirements

CU Boulder faculty and staff can be Principal Investigators (PI) for human subjects research. Graduate students can be PIs for human subjects research, but they must have a CU Boulder

faculty member as a Faculty Advisor. Undergraduate students **cannot** be PIs for human subjects research. A CU Boulder faculty member must be the PI on the project and students can be listed as Co-Investigators.

Investigator Obligations in Conducting Human Research

See POLICY: Investigator Obligations (HRP-070)

See POLICY: Prompt Reporting Requirements (HRP-071)

1. Investigators are expected to be fully aware of and follow all of the requirements described in this manual. The IRB provides further guidance and instruction on its website, which should be used as a resource.
2. Do not start Human Research activities until you have the final IRB Approval Letter.
 - a. Read your Approval Letter carefully. It may contain additional guidance, instructions, or limitations on your research that you will be expected to know and follow.
3. 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 beginning research that involves their resources.
4. 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, funding, and space.
5. Update the IRB Office with any changes to the list of study personnel.
6. Personally conduct and supervise the Human Research.
 - a. Conduct the Human Research in accordance with the current IRB-approved protocol.
 - b. When required by the IRB, ensure that consent is obtained in accordance with the current IRB-approved protocol, using only IRB-approved Consent Document(s).
 - c. Ensure all enrolled participants meet all listed eligibility criteria per the approved protocol document.
 - d. Do not modify the Human Research without prior IRB review and approval unless necessary to eliminate apparent immediate hazards to subjects.
 - e. Protect the rights, safety, and welfare of subjects involved in the research.
7. Submit to the IRB:
 - a. Proposed updates or changes to the study as described in this manual. (See [Submitting an Amendment](#).)
 - b. A Continuing Review or Check-in as requested in the approval letter. (See [Submitting a Continuing Review or Check-in](#).)
 - c. A Final Review when the Human Research is closed. (See [Closing a Study](#).)
8. Report any of the reportable events in [Appendix A](#) to the IRB within five business days. Go to [eRA](#), create a Reportable Event submission, attach all required supplements, and submit.

9. Submit an updated disclosure of financial interests to the Office of Conflicts of Interest (DEPA form) within thirty days of discovering or acquiring (e.g., through purchase, marriage, or inheritance) a new financial interest.
10. Do not accept or provide payments to professionals in exchange for referrals of potential subjects (“finder’s fees”).
11. Do not accept payments designed to accelerate recruitment that were tied to the rate or timing of enrollment (“bonus payments”).
12. See additional requirements of various federal agencies in [Appendix B](#). These represent additional requirements and do not override the baseline requirements of this section.

Research Procedures and/or Study Personnel Outside of CU Boulder

If research procedures take place at a study site outside of CU Boulder or if individuals outside of CU Boulder are engaged in the research, the IRB will require additional information. Please contact the IRB for additional information.

Required Training for Investigators and Study Staff

All members of the research team involved in the design, conduct, or reporting of the research must complete human subjects training via the Collaborative Institutional Training Initiative (CITI) human subjects online training program. The CITI site can be accessed at <http://www.citiprogram.org/>. For more information regarding training requirements, visit the [IRB website](#).

Training is valid for a three-year period, after which time the training must be repeated.

Members of the research team who have not completed human research protections training may not take part in aspects of the research that involve interacting with human subjects and/or their identifiable data.

You may have additional training imposed by other federal, state, or organizational policies.

Submitting New Human Research to the IRB

All applications must be submitted via our electronic system. Go to [eRA](#) and create a New Human Subjects submission. Complete the “Initial Application” eForm, attach all required documents, and submit. Maintain electronic copies of all information submitted to the IRB in case revisions are required. More details of requirements and expectations can be found on the IRB’s website: [Initial Application](#). Instructions for submitting an Initial Application using the eRA system can be found: [eRA Submission Guides](#)

How to Write a Protocol Document

Your research Protocol Document is the official CU Boulder documentation of the study design and procedures that you will carry out in the course of your Human Research. It is critical that this document is complete and accurate with regard to the Human Research that you will conduct, and addresses all regulatory requirements, CU Boulder Policy, and ethical principles that apply to your research. It should be written specifically for this purpose, with the IRB as audience in mind (DO NOT copy directly from a grant proposal or similar document). This document must be used in the

conduct of your research and kept up to date as changes to the research are needed over the lifetime of the study.

You are required to use the most current [Protocol Template](#) applicable to the Regulatory Classification of your research as a starting point for drafting a new study Protocol Document, and reference the instructional information the IRB looks for when reviewing research.

- If the Protocol Document is written paying close attention to the instructions provided, the document will address all regulatory requirements, CU Boulder Policy, and ethical principles that apply to your research.
- The eRA submission system is the official system of record for all your IRB-approved study documents. You must always use the IRB-approved version of the Protocol Document retrieved from the eRA system when making changes to the research.
- Note that, depending on the nature of your research, certain sections of the template may not be applicable to your research. Indicate this as appropriate.
- You may not enroll any individuals who are members of the following populations as subjects in your research unless you indicate this in your inclusion criteria. The inclusion of subjects in these populations has regulatory implications.
 - Adults unable to provide legally effective consent
 - Individuals who are not yet adults (infants, children, teenagers)
 - Pregnant women
 - Prisoners
 - CU Boulder staff, students, and subordinates of Key Personnel

How to Create a Consent Document

You are required to use the most current [consent template](#) applicable to your research, to create a consent document. This template includes the generally required elements of consent, as well as information for specific types of research. Template language is provided for most sections; only include information that is required and/or applicable to your research.

Consent Documents for non-Exempt studies will be dated with an approval date following IRB review and approval. Consent information for studies determined to be Exempt will have an Exempt Determination date. **In either case, you must use the IRB-approved version of any Consent Documents. To ensure only the most recent, correct version of the Consent Document is used, it must be retrieved directly from the Approved Docs screen for the study in eRA.**

In both Exempt and non-Exempt studies, translated versions of Consent Documents must be submitted to and approved by the IRB *prior to use* with any study subject.

Regulatory Classifications

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

- Not “Human Research”: Activities that do not meet the definition of “Human Research” do not fall under IRB oversight (see [Human Research](#) section). Contact the IRB Office if you are uncertain whether an activity is Human Research.

- **“Human research that does not engage the institution”:** Some human research requires review by an IRB, but is not the responsibility of the organization. You may contact the IRB for guidance; review “WORKSHEET: Engagement (HRP-422)” for additional information.
- **Exempt:** Certain categories of Human Research may be exempt from regulation but require IRB review. It is the responsibility of the CU Boulder IRB, not the investigator, to determine whether the research meets an Exempt category. As institutional policy, the CU Boulder IRB will review Exempt studies to ensure they are being ethically conducted. Information required to make this determination will generally be the same as for non-Exempt research. A description of the categories of Exempt research can be found at [45 CFR 46.104](#).
- **Expedited Review:** Certain categories of Human Research are not Exempt but may qualify for review using the Expedited review procedure, meaning that the project may be approved by a single designated IRB reviewer, rather than the convened IRB. A description of research that can be reviewed using the Expedited review procedure can be found on the [Office for Human Research Protections website](#).
- **Review by the Convened IRB:** Non-Exempt Human Research that does not qualify for review using the Expedited procedure must be reviewed by the convened IRB.

IRB Review Decisions

The IRB may approve research, require modifications to the research to secure approval, table research, or disapprove research. The IRB Office will provide you with a letter describing the decision.

- **Approve:** Made when all criteria for approval are met. See “How Review Decisions are Made” below.
- **Modifications Required:** Made when the IRB requires specific modifications to the research before approval can be finalized. The IRB describes the required modifications and gives the investigator an opportunity to respond to the IRB in writing.
- **Defer:** Made when the convened IRB is unable to approve research and the IRB suggests modifications that might make the research approvable. The IRB describes the recommended modifications and gives the investigator an opportunity to respond to the IRB in writing.
- **Incomplete:** Information is missing from the submission and is returned to the investigator.
- **Disapprove:** Made when the convened IRB determines that it is unable to approve research and the IRB cannot describe modifications that might make the research approvable. The IRB describes its reasons for this decision and gives the investigator an opportunity to respond to the IRB in writing.
- **Tabled:** Made when the convened IRB cannot approve the research at a meeting for reasons unrelated to the research, such as loss of quorum. When taking this action, the IRB automatically schedules the research for review at the next available meeting.

In all cases, you have the right to address your concerns to the IRB in person at a convened meeting or with the designated reviewer.

How Review Decisions are Made

Exempt research must meet the requirements outlined in [45 CFR 46.104](#). Non-Exempt research must meet the requirements set forth in [45 CFR 46.111](#).

In order for your research to be reviewed and found to meet the requirements of these regulations, your research submission and documents must be complete, consistent, and clear. Research that is not complete, consistent, and clear will not be approved.

Risk Determinations

The IRB makes risk level determinations based on the definition of “minimal risk” ” as defined in [45 CFR 46.102](#):

“Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”

Research activities that do not meet this definition are considered “more than minimal risk.”

Submitting a Continuing Review or Check-in

Non-Exempt research is required to have either a Continuing Review or Check-in annually. Some research may require a Continuing Review more often than annually. Exempt research is not required to submit either Continuing Review or Check-in. The IRB approval letter clearly states which action is required.

Go to [eRA](#), create a Continuing Review/Check-in submission, complete the “Continuing Review/Check-in” eForm, attach all requested supplements, and submit. Refer to [eRA Submission Guide](#) on the IRB website for detailed instructions.

If a study’s IRB approval expires, all Human Research procedures related to the protocol must cease, including recruitment, advertisement, screening, enrollment, consent, interventions, interactions, and collection or analysis of private identifiable information. Continuing Human Research procedures is a violation of organizational policy. If current subjects will be harmed by stopping Human Research procedures, and there are comparable procedures 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 and there are no comparable procedures available outside the Human Research context, immediately contact the IRB Program Director and provide a written list of the currently enrolled subjects and why they will be harmed by stopping Human Research procedures.

While the IRB will generally send renewal reminders prior to the expiration date of your study, it is the *Principal Investigator’s* personal responsibility to ensure a Continuing Review or Check-in is submitted in sufficient time to allow for IRB review and approval prior to expiration.

Submitting an Amendment

Any change to the IRB-approved research and/or related documents must be reviewed and approved by the IRB *before* the change can be implemented.

Go to [eRA](#), create an Amendment submission, complete the “Amendment” eForm, attach all requested supplements, and submit. Refer to [eRA Submission Guide](#) on the IRB website for detailed instructions. When revising or updating previously approved documents, use versions from the Approved Docs screen for the study in eRA. Research must continue to be conducted without inclusion of the amendment until IRB approval is received. Maintain electronic copies of all information submitted to the IRB in case revisions are required.

Closing a Study

When all Human Research activities, including data analysis, are complete and identifiable data are no longer needed, the study must be closed with the IRB. You are encouraged to deidentify the data at this point. Identifiable data must not be accessed or used for research purposes after study closure.

Go to [eRA](#), create a Final Review submission, complete the “Continuing Review/Check-in” eForm (the same eForm is used for both study closure and Continuing Review/Check-in), attach all requested supplements, and submit. Refer to [eRA Submission Guide](#) on the IRB website for detailed instructions.

Maintaining Records

All study-related documents (Protocol Document, Consent Document, assessment tools, signed consent forms, etc.) must be kept for at least three years after the study is closed with the IRB.

Note that document retention requirements may be longer for FDA regulated research or according to your funding agency.

Additional Information

This document and the [Policies for the Human Research Protection Program](#) are available on the [IRB Web Site](#).

Appendix A: Prompt Reporting Requirements

Report the information items that fall into one or more of the following categories to the IRB within 5 business days:

Information that does not fall under any of these categories does not require reporting to the IRB.

1. Information that indicates a new or increased risk, or a new safety issue, for example:
 - a. New information (e.g., an interim analysis, safety monitoring report, publication 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.
 - b. Protocol violation that harmed subjects or others or that indicates subjects or others might be at increased risk of harm
 - c. Complaint of a subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm
 - d. An investigator brochure, package insert, or device labeling is revised to indicate an increase in the frequency or magnitude of a previously known risk, or describe a new risk
 - e. Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in a research protocol
 - f. Changes significantly affecting the conduct of the clinical trial or increasing the risk to participants
2. Unanticipated Problems. Harm experienced by a subject or other individual, which in the opinion of the investigator is **unexpected** and **probably related** to the research procedures
 - a. A harm is “**unexpected**” when its specificity or severity are inconsistent with risk information previously reviewed and approved by the IRB in terms of nature, severity, frequency, and characteristics of the study population
 - b. A harm is “**probably related**” to the research procedures if in the opinion of the investigator, the research procedures more likely than not caused the harm
3. 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
4. Failure to follow the protocol due to the action or inaction of the investigator or research staff
5. Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject
6. Breach of confidentiality
7. Complaint of a subject that cannot be resolved by the research team
8. Premature suspension or termination by the sponsor, investigator, or institution
9. Incarceration of a subject in a study not approved by the IRB to involve prisoners
10. Audit, inspection, or inquiry by a federal agency and any resulting reports (e.g., FDA Form 483)

11. Written reports of study monitors
12. Unanticipated adverse device effect (any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects)

Appendix B.1: Informed Consent

1. PURPOSE

- 1.1. This guidance describes a process that in general is suitable to obtain informed consent.
- 1.2. Other procedures may be suitable when approved by the IRB.

2. BACKGROUND

- 2.1. "Person providing consent" means:
 - 2.1.1. In the case of a cognitive intact adult, the individual being asked to take part
 - 2.1.2. In the case of an adult unable to consent, that individual's LAR
 - 2.1.3. In the case of a child:
 - 2.1.3.1. One parent, if the other parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.
 - 2.1.3.2. One parent if the IRB determined that permission from one parent was sufficient
 - 2.1.3.3. An individual who is authorized under applicable law to consent on behalf of a child to general medical care
 - 2.1.3.4. Both parents
- 2.2. "Consent information" means:
 - 2.2.1. Long form consent document (when the IRB requires the long form of consent documentation)
 - 2.2.2. Short form consent document and summary (when the IRB allows the short form of consent documentation)
 - 2.2.3. Script or information sheet (when the IRB has approved a waiver of documentation of consent)
- 2.3. Communicate in the preferred language of the person providing consent
- 2.4. Unless the IRB affirmatively approved a protocol to include the following populations, such subjects may not be enrolled:
 - 2.4.1. Adults unable to consent
 - 2.4.2. Children (including neonates)
 - 2.4.3. Neonates of uncertain viability
 - 2.4.4. Nonviable neonates
 - 2.4.5. Pregnant women
 - 2.4.6. Prisoners
 - 2.4.7. Individuals unable to speak English
- 2.5. The short form of consent documentation may be used only if affirmatively approved by the IRB.
- 2.6. For the short form of consent documentation:
 - 2.6.1. The short form is a standard template translated into the subject's language.

- 2.6.2. The summary is the English version of the long form.
- 2.7. For waiver of documentation of consent, the script is the long form without a signature block.
- 2.8. Interpreters are to be conversant in both English and the language understood by the person providing consent. When allowed by institutional policy, the interpreter may be a member of the research team, or a family member or friend of the subject or person providing consent.
- 2.9. If the consent process requires an **Impartial Witness**:
 - 2.9.1. The **Impartial Witness** is to be present during the entire consent discussion and to attest that the information in the consent document and any other information provided was accurately explained to, and apparently understood by, the subject/LAR, and that consent was freely given.
 - 2.9.2. The **Impartial Witness** may not be a person involved in the research.

3. GUIDANCE

- 3.1. Obtain the IRB-approved consent document, short form consent document, or script, as applicable.
 - 3.1.1. Verify that you are using the most current IRB-approved information.
 - 3.1.2. Verify that the consent document, if any, is in language understandable to the person providing consent.
- 3.2. If the person providing consent cannot read or the short form of consent documentation is used, obtain an **Impartial Witness**.
- 3.3. If the person providing consent cannot speak English, obtain the services of an interpreter.
- 3.4. Go over the information in the consent document using language understandable to the person providing consent.
 - 3.4.1. Do not provide any information to the person providing consent through which the person providing consent is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.
 - 3.4.2. When providing information about treatments or compensation for injury, provide factual information and avoid statements that imply that compensation or treatment is never available.
- 3.5. Invite and answer questions.
- 3.6. Evaluate whether the following is true for the person providing consent. If not, take steps to correct or determine that the person providing consent is incapable of providing consent:
 - 3.6.1. The person providing consent has been provided sufficient information.
 - 3.6.2. The person providing consent understands the information
 - 3.6.2.1. If the person providing consent has a disease or condition that may affect cognition, assess whether the person providing

- consent has sufficient cognitive capacity to legally provide informed consent.
- 3.6.2.2. If the subject is pregnant, ensure the person providing consent is fully informed regarding the reasonably foreseeable effect of the research on the fetus or neonate.
 - 3.6.3. The person providing consent does not feel coerced or unduly influenced.
 - 3.6.3.1. Ensure there is no threat of harm or adverse consequences for a decision to not participate.
 - 3.6.3.2. Ensure that outside parties (family or caretakers) do not coerce or unduly influence the person providing consent, especially if that person is vulnerable to coercion or undue influence.
 - 3.6.3.3. Ensure that the amount of payment does not coerce or unduly influence economically disadvantaged individuals.
 - 3.6.3.4. For persons providing consent who are in a subordinate position to a member of the research team (e.g., employee or student), ensure that there is no threat of harm or adverse consequences to the subject's position for a decision to not participate.
 - 3.6.4. The person providing consent has sufficient time to make a decision.
 - 3.6.4.1. Provide the person providing consent with sufficient time to understand the information. Spend as much time as needed.
 - 3.6.4.2. Provide the person providing consent with sufficient time to ask questions.
 - 3.6.5. The individual providing consent understands the consequences of a decision.
 - 3.6.6. The individual providing consent can communicate a choice.
 - 3.7. Once a person providing consent indicates that he or she does not want to consent, stop.
 - 3.8. If the subject is a child or adult unable to consent:
 - 3.8.1. Explain the research to the extent compatible with the subject's understanding.
 - 3.8.1.1. Ensure that parents or guardians do not coerce or unduly influence children.
 - 3.8.1.2. Ensure that outside parties (family or caretakers) do not coerce or unduly influence adults unable to consent.
 - 3.8.2. If the IRB determined that assent was a requirement and the subject is capable of being consulted, request the assent (affirmative agreement) of the subject.
 - 3.8.2.1. If the subject indicates that he or she does not want to take part, stop.

4. REFERENCES

- 4.1. 21 CFR §50.20, §50.25

Appendix B.2: Documentation of Informed Consent

1. PURPOSE

- 1.1. This guidance describes a process that in general is suitable to document consent in writing.
- 1.2. Other procedures may be suitable when approved by the IRB.

2. BACKGROUND

- 2.1. "Person providing consent" means:
 - 2.1.1. In the case of a cognitive intact adult, the individual being asked to take part
 - 2.1.2. In the case of an adult unable to consent, that individual's LAR
 - 2.1.3. In the case of a child:
 - 2.1.3.1. One parent, if the other parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.
 - 2.1.3.2. One parent if the IRB determined that permission from one parent was sufficient
 - 2.1.3.3. An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care
 - 2.1.3.4. Both parents
- 2.2. The short form of consent documentation may be use only if affirmatively approved by the IRB.
- 2.3. For the short form of consent documentation:
 - 2.3.1. The short form is a standard template translated into the subject's language.
 - 2.3.2. The summary is the English version of the long form.
- 2.4. If the consent process required an **Impartial Witness**:
 - 2.4.1. The **Impartial Witness** is to be present during the entire consent discussion and to attest that the information in the consent document and any other information provided was accurately explained to, and apparently understood by, the subject/LAR, and that consent was freely given.
 - 2.4.2. The **Impartial Witness** may not be a person involved in the research.
- 2.5. For FDA regulated research:
 - 2.5.1. The assent of a child will be documented using a separate assent form.

3. GUIDANCE

- 3.1. If the consent process will be documented with the long form:
 - 3.1.1. Verify that the document is in language understandable to the person providing consent.
 - 3.1.2. If the IRB required written documentation of assent, note one of the following:
 - 3.1.2.1. Assent of the child was obtained.

- 3.1.2.2. Assent of the child was not obtained because the capability of the child is so limited that the child cannot reasonably be consulted.
 - 3.1.3. Have the following individuals personally sign and date the consent document:
 - 3.1.3.1. Person giving consent
 - 3.1.3.2. Person obtaining consent
 - 3.1.3.3. **Impartial Witness**, if any
 - 3.2. If the consent process will be documented with the short form:
 - 3.2.1. Verify that the document is in language understandable to the person providing consent.
 - 3.2.2. If the IRB required written documentation of assent, note one of the following:
 - 3.2.2.1. Assent of the child was obtained.
 - 3.2.2.2. Assent of the child was not obtained because the capability of the child is so limited that the child cannot reasonably be consulted.
 - 3.2.3. Have the following individuals personally sign and date the consent document:
 - 3.2.3.1. Person giving consent
 - 3.2.3.2. Person obtaining consent
 - 3.2.3.3. **Impartial Witness**, if any
 - 3.2.4. Have the following individuals personally sign and date the summary:
 - 3.2.4.1. Person giving consent
 - 3.2.4.2. Person obtaining consent
 - 3.2.4.3. **Impartial Witness**, if any
- 3.3. Provide the person providing consent with copies of the signed and dated documents.
 - 3.3.1. This may be accomplished either by making a photocopy or by having individuals sign and date two copies.
- 3.4. File a copy of the consent document with the medical record when required by local policy.
- 3.5. Retain the signed and dated documents in the study records for the greater of:
 - 3.5.1. Three years after completion of the research
 - 3.5.2. For drug studies conducted under an IND, two 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 two years after the investigation is discontinued and FDA is notified.
 - 3.5.3. For device studies conducted under an IDE or abbreviated IDE, two years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no

longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

- 3.5.4. The retention period requested by the sponsor.
- 3.5.5. The retention period required by local, state, or international law.
- 3.5.6. The retention period required by a site that is not part of this [Organization].

4. REFERENCES

- 4.1. 21 CFR §50.27, 56.115(b), §312.62(c), §812.140(d)
- 4.2. 45 CFR §46.115(b), §46.117

Appendix B.3: Deception

A fundamental pillar of human subject research is informed consent; that subjects in research must make a free, voluntary, and fully-informed decision about whether to participate in research.

Deception in research involves any attempts to mislead research subjects, whether actively or passively, in order to prevent biasing research outcomes. Deception can be an important tool in behavioral research when subjects' behavior might be altered by full knowledge of what is being studied and/or the study's methods.

"Deception" is an umbrella term encompassing two main types of misleading actions:

- 1) **Active misleading** (e.g., misdirecting, lying) of subjects, where the researcher provides subjects with false information about themselves or research procedures in order to study their behavior in an unbiased way.
- 2) **Passive misleading** of subjects, where researcher withholds key information (including that they are in a research study), or the true reason for conducting the research, in order to study their behavior in an unbiased way.

Either form of deception requires special considerations by the IRB, and usually requires the research to meet criteria to waive informed consent. Here are some key points about using deception in research:

- Only minimal risk research can qualify for deception, and the manner in which subjects are deceived must constitute minimal risk. If the research poses greater than minimal risk to subjects, an alternative strategy that fully informs subjects of study purposes and procedures must be used.
- When deception is employed in research, subjects must be notified at the earliest possible time point about the deception, when such debriefing is feasible. During debriefing, subjects must be given the opportunity to withdraw from the research and exclude their data from study analyses.
- If possible, researchers should inform subjects that they might be deceived, or not always provided with full information, during the research. If the research is exempt, this is a requirement.

For further information about the use of deception in research, please see CU Boulder IRBs full [guidance document](#) on deception.

Appendix B.4: Safety Monitoring Plans in Protocols

Research that poses **minimal risk** to subjects does not require a formal safety monitoring plan in the protocol, but should still have a statement that the PI will monitor the research for any unanticipated problems (e.g., breach of confidentiality or other unexpected events). Research that is **greater than minimal risk** requires a protocol section describing of how safety of participants and the trial will be monitored. The protocol safety monitoring plan should address several key questions:

1) What will be monitored?

When writing your protocol, you have an initial estimate of what the risks of the research will be. How, then, will you ensure your risk estimate was accurate as the study proceeds? Identify the key metrics that must be monitored (e.g., rates of adverse events, unexpected adverse events, vital signs, key lab tests that must be followed) to ensure the risks to subjects are minimized and in line with the estimates detailed in the protocol.

2) Who will perform monitoring and how frequently?

The individual(s) responsible for monitoring safety during the study should be clearly identified. It is important to ensure these individuals have the appropriate background and expertise to monitor safety. If adverse events of a medical nature are expected, there should be an investigator with a clinical background to properly assess the adverse events. Such qualified investigators may need to be present during particular high-risk procedures. For larger studies, or studies with high or novel risks, consider including an independent safety officer or a safety monitoring committee. It is important to specify how frequently formal safety monitoring activities will occur (e.g., constant monitoring during the high-risk procedure and at least every 6 months for routine safety committee meetings).

3) How will problems be triaged and internally communicated?

If a safety monitor or safety committee will not be present during research procedures, a clear plan for how adverse events will be identified, triaged, and communicated to the qualified safety monitor is critical. Who will be notified, when they will be notified, and by what means need to be mapped out to ensure there is no delay in evaluating the safety of subjects during the study.

4) What emergency procedures are in place?

If there is any chance of a life-threatening adverse event occurring during study procedures, it is critical to describe the emergency response procedures available in the location procedures are being performed. If study procedures will take place in multiple locations, emergency response at each location may differ and must be detailed.

Appendix B.5: FDA-regulated research (drugs and devices)

Most research where subjects receive drugs, and some research utilizing devices, will fall under regulation by the Food and Drug Administration (FDA). Because there are special rules governing these types of research studies, you are strongly encouraged to contact the IRB office to discuss your research before submitting your protocol if you are using drugs or devices.

The following are some key points relating to drugs and devices in research:

1. Drugs in research

If your protocol describes giving subjects a drug of any kind, the research will be subject to FDA regulations. *It does not matter whether research goals include evaluating the drug;* even giving a subject a drug in order to study a resulting physiologic effect is considered 'drug research' to the FDA.

- Some studies giving drugs to subjects will require special permission from the FDA (an 'IND submission') before they can be approved by the IRB.
- Contact the IRB before submitting your protocol to see if an IND submission is likely to be required.

2. Devices in research

In contrast to drugs, you must be studying the device itself for the research to be FDA-regulated. *Studying the device* means collecting data on a device's **effectiveness** (its ability to perform a certain function) and/or **safety** (its safety to humans in performing its function). The following are some high-level summary points regarding device research; please also see the [guidance document](#) on the IRB website regarding investigational device studies.

- For studies collecting safety or effectiveness data on a device, a nuanced categorization of the device research must occur. **You are encouraged to contact the IRB office before submitting your protocol to get advanced advice on how to provide key information to the IRB.**
- Some device studies might be exempt from the FDA device regulations.
- If the study is not exempt, then:
 - Your research will need to be reviewed by the full IRB committee, even if the research and the device pose only minimal risk to subjects.
 - Additional requirements must be followed during the research (e.g., certain types of record-keeping, adhering specific labels to the device, etc.)
 - You must include in your protocol a statement about whether the device is a significant-risk (SR) device or a non-significant risk (NSR) device. A device, **given how it is used in the specific study**, is NSR if it does not meet the following significant-risk definition:
 - Device is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
 - Device is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;

- Device is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
 - Device otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- Special permission from the FDA (an 'IDE submission') may be required before the research can be approved by the IRB.

Appendix C.1: Additional Obligations – DoD

1. PURPOSE

- 1.1. This guidance outlines the additional obligations of investigators conducting research supported or conducted by DOD.

2. GUIDANCE

2.1. Training and education

- 2.1.1. All personnel who conduct, review, approve, oversee, support, or manage human subjects research are required to undergo initial and continuing research ethics education.
- 2.1.2. There may be specific DOD educational requirements or certification required.
- 2.1.3. DOD may evaluate the organization's education policies to ensure the personnel are qualified to perform the research, based on the complexity and risk of the research.
- 2.1.4. As the investigator, you must be aware of the specific requirements contained in DOD regulations and requirements and educated about these requirements when appropriate.
- 2.1.5. Civilian researchers attempting to access military volunteers should seek collaboration with a military researcher familiar with service specific requirements.

2.2. Scientific Review

- 2.2.1. The IRB must consider the scientific merit of the research.
- 2.2.2. The IRB may rely on outside experts to provide an evaluation of the scientific merit of the research. Pls must submit a [Scientific Merit Review Letter](#).

2.3. International Research

- 2.3.1. You or the organization must obtain permission to conduct research in that country by certification or local ethics review.
- 2.3.2. You must follow all local laws, regulations, customs, and practices.

2.4. Reporting: The following findings in DOD-supported research must be reported to the DOD human research protection officer within 30 days:

- 2.4.1. Determinations of **Serious Noncompliance** or **Continuing Noncompliance**
- 2.4.2. Significant changes to the research protocol that are approved by the IRB
- 2.4.3. The results of the IRB continuing review
- 2.4.4. Change of reviewing IRB
- 2.4.5. When the organization is notified by any Federal department, agency or national organization that any part of an HRPP is under investigation for cause requirements
- 2.4.6. **Unanticipated Problems Involving Risk to Subjects or Others**
- 2.4.7. **Suspension of IRB approval**
- 2.4.8. **Termination of IRB approval**

2.5. Survey Approval

- 2.5.1. Surveys performed on DOD personnel must be submitted, reviewed, and approved by the DOD after the research protocol is approved by the IRB. When a survey crosses DOD Components, additional review is required.

2.6. Multisite Research

- 2.6.1. When conducting multi-site research, a formal agreement between organizations is required to specify the roles and responsibilities of each party.

2.7. Definition of **Minimal Risk**

- 2.7.1. The definition of the minimal risk based on the phrase “ordinarily encountered in daily life or during the performance of routine physical or physiological examinations or tests” must not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain). The CU Boulder IRB applies a healthy-person standard to risks “ordinarily encountered in daily life or during the performance of routine physical or physiological examinations or tests.”
- 2.7.2. The organization applies this definition to all research regardless of funding.

2.8. Appointment of a Research Monitor:

- 2.8.1. This is required for research involving greater than minimal risk.
- 2.8.2. The IRB or institutional official can require a research monitor for a portion of the research or studies involving no more than minimal risk, if appropriate.
- 2.8.3. The research monitor is appointed by name and must be independent of the team conducting the research.
- 2.8.4. There may be more than one research monitor (e.g. if different skills or experience are needed).
- 2.8.5. The monitor may be an ombudsman or a member of the data safety monitoring board. The IRB must approve a written summary of the monitors’ duties, authorities, and responsibilities.
- 2.8.6. The IRB or institutional official must communicate with research monitors to confirm their duties, authorities, and responsibilities.
- 2.8.7. The duties of the research monitor are determined on the basis of specific risks or concerns about the research.
 - 2.8.7.1. The research monitor may perform oversight functions (e.g., observe recruitment, enrollment procedures, and the consent process, oversee study interventions and interactions, review monitoring plans and **Unanticipated Problems Involving Risk to Subjects or Others**, oversee data matching, data collection and analysis).

- 2.8.7.2. The research monitor may discuss the research protocol with investigators, interview human subjects, and consult with others outside of the study.
- 2.8.7.3. Report observations and findings to the IRB or a designated official.
- 2.8.8. The research monitor has the authority to:
 - 2.8.8.1. Stop a research study in progress.
 - 2.8.8.2. Remove individuals from study.
 - 2.8.8.3. Take any steps to protect the safety and well-being of subjects until the IRB can assess.
- 2.8.9. Recruitment of Service Members
 - 2.8.9.1. Superiors of service members are not permitted to influence the decision of their subordinates.
 - 2.8.9.2. Superiors of service members in the chain of command may not be present at the time of recruitment.
 - 2.8.9.3. Officers and senior non-commissioned officers have a separate opportunity to participate.
- 2.8.10. When recruitment involves group setting, the IRB may require that an independent ombudsman is present.
- 2.8.11. Compensation of Service Members:
 - 2.8.11.1. Service member may not receive pay or compensation for research during duty hours.
 - 2.8.11.2. A service member may be compensated for research if the subject is involved in the research when not on duty.
 - 2.8.11.3. Federal employees while on duty and non-Federal persons may be compensated for blood draws for research up to \$50 for each blood draw.
 - 2.8.11.4. Non-Federal persons may be compensated for participating in research involving other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research.
- 2.9. Consent
 - 2.9.1. The disclosure for research-related injury must follow the requirements of the DOD component.
 - 2.9.2. If the subject undergoes interactions or interventions for research purposes, the subject is considered an “experimental subject.” For experimental subjects:
 - 2.9.2.1. A waiver of the consent process is prohibited unless a waiver is obtained from the Assistant Secretary of DOD for Research and Engineering.

- 2.9.2.2. The Assistant Secretary for DOD for Research and Engineering may waive the requirements for consent when all of the following are met:
 - 2.9.2.2.1. The research is necessary to advance the development of a medical product for the Military Services.
 - 2.9.2.2.2. The research may directly benefit the individual experimental subject.
 - 2.9.2.2.3. The research is conducted in compliance with all other applicable laws and regulations.
- 2.9.2.3. The IRB may waive the consent process for subjects who are not “experimental subjects.”
- 2.9.2.4. If consent is to be obtained from the experimental subjects’ legal representative, the research must intend to benefit the individual subject.
 - 2.9.2.4.1. The determination that research is intended to be beneficial to the individual experimental subject must be made by an IRB.

2.9.3. Waivers of consent are prohibited for classified research.

2.10. Research on Pregnant Women

- 2.10.1. Research involving pregnant women and fetuses as subjects is subject to HHS Subpart B except:
 - 2.10.1.1. The phrase “biomedical knowledge” is replaced with “generalizable knowledge.”
 - 2.10.1.2. The applicability of Subpart B is limited to research involving pregnant women as subjects in research that is more than minimal risk and included interventions or invasive procedures to the woman or the fetus or involving fetuses or neonates as subjects.

2.11. Research on Prisoners

- 2.11.1. Research involving prisoners is subject to HHS Subparts C.
- 2.11.2. Research involving prisoners cannot be reviewed by the expedited procedure.
- 2.11.3. When the IRB reviews research involving prisoners, at least one prisoner representative must be present for quorum.
- 2.11.4. In addition to allowable categories of research on prisoners in Subpart C, epidemiological research is also allowable when:
 - 2.11.4.1. The research describes the prevalence or incidence of a disease by identifying all cases or studies potential risk factor association for a disease.
 - 2.11.4.2. The research presents no more than minimal risk.

- 2.11.4.3. The research presents no more than an inconvenience to the subject.
- 2.11.5. When a subject becomes a prisoner, if the investigator asserts to the IRB that it is in the best interest of the prisoner-subject to continue to participate in the research while a prisoner, the IRB chair may determine that the prisoner-subject may continue to participate until the convened IRB can review this request to approve a change in the research protocol and until the institutional official and DOD Component office review the IRB's approval to change the research protocol. Otherwise, the IRB chair must require that all research interactions and interventions with the prisoner-subject (including obtaining identifiable private information) cease until the convened IRB can review this request to approve a change in the research protocol. The convened IRB, upon receipt of notification that a previously enrolled human subject has become a prisoner, must promptly re-review the research protocol to ensure that the rights and wellbeing of the human subject, now a prisoner, are not in jeopardy. The IRB should consult with a subject matter expert having the expertise of a prisoner representative if the IRB reviewing the research protocol does not have a prisoner representative. If the prisoner-subject can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner-subject's confinement does not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research involving human subjects from continuing as approved, the convened IRB may approve a change in the study to allow this prisoner-subject to continue to participate in the research. This approval is limited to the individual prisoner-subject and does not allow recruitment of prisoners as subjects.
- 2.11.6. Research involving a detainee as a human subject is prohibited.
 - 2.11.6.1. This prohibition does not apply to research involving investigational drugs and devices when the same products would be offered to US military personnel in the same location for the same condition.
- 2.11.7. Research involving prisoners of war is prohibited.
 - 2.11.7.1. "Prisoner of war" includes any person captured, detained, held, or otherwise under the control of DOD personnel (military, civilian, or contractor employee). Such persons include: Enemy Combatant, Lawful Enemy Combatant, Unlawful Enemy Combatant, Enemy Prisoner of War, Retained Person, and Civilian Internee. Such persons do not include personnel of the DOD being held for law enforcement purposes. It does not include persons being held primarily for law enforcement purposes, except where the United States is the occupying power.
 - 2.11.7.2. This prohibition does not apply to activities covered by investigational new drug or investigational device provisions for

the purpose of diagnosis or treatment of a medical condition in a patient. Such treatment (e.g., an investigational new drug) may be offered to detainees with the detainees' informed consent when the medical products are subject to FDA regulations for investigational new drugs or investigational medical devices, and only when the same product would be offered to members of the U.S. Military Services in the same location for the same medical condition and only when consistent with established medical practice involving investigational drugs and devices.

2.12. Research on Children

- 2.12.1. Research involving children is subject to the HHS Subpart D.
- 2.12.2. The exemption for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

2.13. Research on Fetal Tissue

- 2.13.1. Fetal research must comply with US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g.

2.14. Waiver of Informed consent for Planned Emergency Research

- 2.14.1. An exception from consent in emergency medicine research is prohibited unless a waiver is obtained from the Secretary of DOD.

2.15. Records

- 2.15.1. Records maintained that document compliance or **Noncompliance** with DOD regulations must be made accessible for inspection and copying by representatives of the DOD at reasonable times and in a reasonable manner as determined by the supporting DOD component.

2.16. Non-exempt Classified Research

- 2.16.1. The involvement of classified information may be limited to information needed for IRB approval and oversight of the research; information needed to inform the human subjects during the consent process and Information provided by the subjects during the course of the research.
- 2.16.2. Secretary of DOD approval is required for all classified non-exempt research involving subjects.
 - 2.16.2.1. Submission for approval must be from the Head of the OSD or DOD Component conducting or supporting the non-exempt research involving human subjects. The request must be coordinated with the ASD(R&E) and General Counsel of the Department of DOD after the IRB has approved the research.
- 2.16.3. Waivers of informed consent are prohibited.
- 2.16.4. Informed consent procedures must include:

- 2.16.4.1. Identification of the DOD as the supporting institution of the research, unless the research involves no more than minimal risk. The Secretary of DOD may grant an exception to this requirement on the grounds that providing this information could compromise intelligence sources or methods.
- 2.16.4.2. A statement that the research involving human subjects is classified and an explanation of the impact of the classification.
- 2.16.5. IRB approval process must meet the following requirements:
 - 2.16.5.1. IRB review must be conducted using a full board review. Use of an expedited review procedure is prohibited.
 - 2.16.5.2. At least one non-affiliated member must be a non-Federal employee (other than as an individual appointed as an expert or consultant for purposes of service on the IRB).
 - 2.16.5.3. Any IRB member who disagrees with a majority decision approving a project may appeal the decision to the Secretary of DOD. The appeal must be included in the DOD Component's submission to the Secretary of DOD.
 - 2.16.5.4. The IRB must determine whether potential subjects need access to classified information to make a valid, informed consent decision.
- 2.16.6. Disclosure or use of classified information must comply with DOD requirements for access to and protection of classified information.

3. REFERENCES

- 3.1. 10 USC 980
- 3.2. DOD Instruction 3216.02
- 3.3. DOD Instruction 3216.2
- 3.4. OPNAVINST 5300.8B
- 3.5. SECNAVINST 3900.39D

Appendix C.2: Additional Obligations – DOE

1. PURPOSE

- 1.1. This guidance outlines the additional obligations of investigators conducting research supported or conducted by DOE.

2. GUIDANCE

- 2.1. DOE-funded or DOE laboratory-managed or conducted projects involving intentional modification of an individual's or a group of individuals' environment must be managed as human subjects research and subject to the requirements of DOE Order 443.1B.
 - 2.1.1. Where "generalizable" should be viewed in terms of contribution to knowledge within the specific field of study, this includes:
 - 2.1.1.1. Studies in human environments (e.g., occupied homes and offices, classrooms, and transit centers like subway systems and airports) that use tracer chemicals, particles, and/or other materials, such as perfluorocarbons, to characterize airflow.
 - 2.1.1.2. Studies in occupied homes and/or offices that:
 - 2.1.1.2.1. Manipulate the environment to achieve research aims, e.g., increasing humidity and/or reducing influx of outside air through new energy-saving ventilation systems.
 - 2.1.1.2.2. Test new materials (e.g., sequentially changing the filter materials in the HVAC system while monitoring the effects on air quality and energy use).
 - 2.1.1.2.3. 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. Some surveys may be online surveys administered through providers such as Amazon Mechanical Turk and Survey Monkey.
 - 2.1.2. Even if the IRB does not view a project as meeting the literal definition of human subjects research as defined in 45 CFR Part 46, DOE requires initial review by the IRB of the application and supporting materials to determine whether the individuals included in the research will be properly informed and protected. Adherence to each specific requirement of 45 CFR Part 46 is not required in such a case, but DOE does require that:
 - 2.1.2.1. An application and supporting materials be submitted to the IRB;
 - 2.1.2.2. The Chair decide the level of review;
 - 2.1.2.3. During the review, the IRB assess risks associated with the research and whether the individuals to be included in such

research will be properly informed and protected. SMEs should be used, as needed, in assessing risks and in determining whether risks have been mitigated to the extent practicable (to minimal risk).

- 2.1.2.4. After the review, the Chair send a letter to the PI indicating that the project has been reviewed in accordance with DOE expectations and will be monitored and tracked by the IRB, which means that the PI will:
 - 2.1.2.4.1. Implement any IRB recommendations before the project begins;
 - 2.1.2.4.2. Notify the IRB of any proposed changes to the protocol in the future and ensure IRB review and authorization to proceed before implementing these changes;
 - 2.1.2.4.3. Provide an annual update to the IRB; and
 - 2.1.2.4.4. Follow the notification and reporting requirements in DOE O 443.1B for reporting adverse events, annual update of the DOE HSRD, etc.
- 2.2. Within 48 hours of the following (or within 24 hours if private identifiable information is involved), provide a description of corrective actions taken immediately following the incident, as well as corrective actions to be taken for concurrence by the appropriate DOE HRPP Manager:
 - 2.2.1. Any significant adverse events, unanticipated problems, and complaints about the research,
 - 2.2.2. Any **Suspension of IRB Approval Termination of IRB Approval**;
 - 2.2.3. Any significant **Noncompliance** with HRPP procedures or other requirements, which shall be reported to the IRB for evaluation for further action with the appropriate DOE Human Subject Protection Program Manager
- 2.3. In accordance with the DOE “Checklist for IRBs to Use in Verifying that HS Research Protocols are In Compliance with DOE Requirements,” your research protocol must include description of processes for:
 - 2.3.1. Keeping private identifiable information confidential
 - 2.3.2. Releasing private identifiable information only under a procedure approved by the responsible IRB(s) and DOE, where required
 - 2.3.3. Using private identifiable information only for purposes of the DOE-approved research
 - 2.3.4. Handling and marking documents containing private identifiable information as “containing private identifiable information” or “containing protected health information”
 - 2.3.5. Establishing reasonable administrative, technical, and physical safeguards to prevent unauthorized use or disclosure of private identifiable information

- 2.3.6. Making no further use or disclosure of the private identifiable information except when approved by the responsible IRB and DOE, where applicable, and then only:
 - 2.3.6.1. In an emergency affecting the health or safety of any individual
 - 2.3.6.2. For use in another research project under these same conditions and with DOE written authorization
 - 2.3.6.3. For disclosure to a person authorized by the DOE program office for the purpose of an audit related to the project or when required by law.
- 2.3.7. Protecting private identifiable information data stored on removable media using encryption products that are Federal Information Processing Standards (FIPS) 140-2 certified
- 2.3.8. Using FIPS 140-2 certified encryption that meet the current DOE password requirements cited in DOE Guide 205.3-1
- 2.3.9. Shipping removable media containing PII, as required, by express overnight service with signature and tracking capability, and shipping hard copy documents double wrapped via express overnight service
- 2.3.10. Encrypting data files containing PII that are being sent by e-mail with FIPS 140-2 certified encryption products
- 2.3.11. Sending passwords that are used to encrypt data files containing PII separately from the encrypted data file, i.e. separate e-mail, telephone call, separate letter
- 2.3.12. Using FIPS 140-2 certified encryption methods for websites established for the submission of information that includes PII
- 2.3.13. In addition to other reporting requirements, reporting the loss or suspected loss of PII immediately (within 5 business days) upon discovery to: 1) the DOE Project Officer and 2) the applicable IRBs.

3. REFERENCES

- 3.1. 10 CFR 745
- 3.2. DOE Order 443.1.B
- 3.3. Checklist for IRBs to Use in Verifying That HS Research Protocols Are in Compliance with DOE Requirements

Appendix C.3: Additional Obligations – DOJ

1. PURPOSE

- 1.1. This guidance outlines the additional obligations of investigators conducting research supported or conducted by DOJ.

2. GUIDANCE

- 2.1. National Institute of Justice (NIJ)-funded research
 - 2.1.1. Investigators must have a privacy certificate approved by the NIJ human subjects protection officer.
 - 2.1.2. Investigators and research staff must sign employee confidentiality statements, and investigators must maintain these statements.
 - 2.1.3. Investigators must obtain written informed consent and disclose
 - 2.1.3.1. The names of the funding agencies.
 - 2.1.3.2. A statement describing the extent to which confidentiality of records identifying the subject will be maintained.
 - 2.1.3.3. Private, identifiable information will be kept confidential and will only be used for research and statistical purposes or if, due to sample size or some unique feature, the identity of the individual cannot be maintained, a statement to that effect.
 - 2.1.3.3.1. What information will be disclosed, under what circumstances, and to whom.
 - 2.1.3.3.2. Any risks that might result from this disclosure
 - 2.1.3.4. The research team cannot report child abuse unless the subject signs another consent document to allow child abuse reporting.
 - 2.1.4. Investigators must send to the National Archive of Criminal Justice Data a de-identified copy of all data with copies of the informed consent document, data collection instruments, surveys, or other relevant research materials.
- 2.2. Research conducted within the Bureau of Prisons
 - 2.2.1. The Department of Justice does not consider implementation of Bureau of Prisons programmatic or operational initiatives made through pilot projects to be research.
 - 2.2.2. Investigators must follow the requirements of 28 CFR 512, including:
 - 2.2.2.1. The research must not involve medical experimentation, cosmetic research, or pharmaceutical testing.
 - 2.2.2.2. The research design must be compatible with both the operation of prison facilities and protection of human subjects.
 - 2.2.2.3. The investigator must observe the rules of the institution or office in which the research is conducted.
 - 2.2.2.4. Any investigator who is not an employee of the Bureau of Prisons must sign a statement in which the investigator agrees to adhere to the requirements of 28 CFR 512.

- 2.2.2.5. The Bureau of Prisons IRB must approve the research.
- 2.2.2.6. The research must have an adequate research design and contribute to the advancement of knowledge about corrections.
- 2.2.2.7. The selection of subjects within any one organization must be equitable.
- 2.2.2.8. Incentives may not be offered to help persuade inmate subjects to participate. Soft drinks and snacks to be consumed at the test setting may be offered.
- 2.2.2.9. Reasonable accommodations such as nominal monetary recompense for time and effort may be offered to non-confined research subjects who are both:
 - 2.2.2.9.1. No longer in Bureau of Prisons custody
 - 2.2.2.9.2. Participating in authorized research being conducted by Bureau of Prisons employees or contractors
- 2.2.2.10. A non-employee of the Bureau of Prisons 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.
- 2.2.2.11. Except as noted in the consent statement to the subject, the investigator 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.
- 2.2.2.12. 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.
- 2.2.2.13. If the investigator is conducting a study of special interest to the Office of Research and Evaluation (ORE) but the study is not a joint research involving ORE, the investigator may be asked to provide ORE with the computerized research data, not identifiable to individual subjects, accompanied by detailed documentation. These arrangements must be negotiated prior to the beginning of the data collection phase of the research.
- 2.2.2.14. Consent documents must disclose:
 - 2.2.2.14.1. Identification of the investigators.
 - 2.2.2.14.2. Anticipated uses of the results of the research.
 - 2.2.2.14.3. A statement that participation is completely voluntary and that the subject may withdraw consent and end participation in the research at

- any time without penalty or prejudice (the inmate will be returned to regular assignment or activity by staff as soon as practicable).
- 2.2.2.14.4. 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.
 - 2.2.2.14.5. A statement that participation in the research will have no effect on the inmate subject's release date or parole eligibility.
- 2.2.3. Investigators must have academic preparation or experience in the area of study of the proposed research.
- 2.2.4. When submitting a research protocol, investigators must provide the following information:
- 2.2.4.1. A summary statement, which includes:
 - 2.2.4.1.1. Names and current affiliations of the investigators.
 - 2.2.4.1.2. Title of the study.
 - 2.2.4.1.3. Purpose of the study.
 - 2.2.4.1.4. Location of the study.
 - 2.2.4.1.5. Methods to be employed.
 - 2.2.4.1.6. Anticipated results.
 - 2.2.4.1.7. Duration of the study.
 - 2.2.4.1.8. Number of subjects (staff or inmates) required and amount of time required from each.
 - 2.2.4.1.9. Indication of risk or discomfort involved as a result of participation.
 - 2.2.4.2. A comprehensive statement, which includes:
 - 2.2.4.2.1. Review of related literature.
 - 2.2.4.2.2. Detailed description of the research method.
 - 2.2.4.2.3. Significance of anticipated results and their contribution to the advancement of knowledge.
 - 2.2.4.2.4. Specific resources required from the Bureau of Prisons.
 - 2.2.4.2.5. 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.

- 2.2.4.2.5.1. Description of steps taken to minimize any risks.
- 2.2.4.2.6. Description of physical or administrative procedures to be followed to:
 - 2.2.4.2.6.1. Ensure the security of any individually identifiable data that are being collected for the study.
 - 2.2.4.2.6.2. Destroy research records or remove individual identifiers from those records when the research has been completed.
- 2.2.4.2.7. Description of any anticipated effects of the research study on organizational programs and operations.
- 2.2.4.2.8. Relevant research materials such as vitae, endorsements, sample consent statements, questionnaires, and interview schedules.
- 2.2.4.2.9. A statement regarding assurances and certification required by federal regulations, if applicable.
- 2.2.5. Investigators must assume responsibility for actions of any person engaged to participate in the research as an associate, assistant, or subcontractor to the investigator.
- 2.2.6. At least once a year, investigators must provide the Chief, Office of Research and Evaluation, with a report on the progress of the research.
- 2.2.7. At least 12 working days before any report of findings is to be released, investigators must distribute one copy of the report with an abstract in the report of findings to each of the following:
 - 2.2.7.1. The chairperson of the Bureau Research Review Board
 - 2.2.7.2. The regional director
 - 2.2.7.3. The warden of each institution that provided data or assistance
- 2.2.8. In any publication of results, investigators must acknowledge the Bureau's participation in the research.
- 2.2.9. Investigators expressly disclaim approval or endorsement of the published material as an expression of the policies or views of the Bureau.
- 2.2.10. Prior to submitting for publication the results of research conducted under this subpart, investigators must provide two copies of the material, for informational purposes only, to the Chief, Office of Research and Evaluation, Central Office, Bureau of Prisons.

3. REFERENCES

- 3.1. 28 CFR §22,
- 3.2. 28 CFR §512

Appendix C.4: Additional Obligations – Department of Education

1. PURPOSE

- 1.1. This guidance outlines the additional obligations of investigators conducting research supported or conducted by ED.

2. GUIDANCE

- 2.1. For research funded by the National Institute on Disability and Rehabilitation Research, when the IRB reviews research that purposefully requires inclusion of children with disabilities or individuals with mental disabilities as research subjects, the IRB includes at least one person primarily concerned with the welfare of these research subjects.
- 2.2. The Family Educational Rights and Privacy Act (FERPA) applies when investigators obtain student records or personal education information from an education program as defined as any program principally engaged in the provision of education, including, but not limited to, early childhood education, elementary and secondary education, postsecondary education, special education, job training, career and technical education, and adult education. FERPA requirements include:
 - 2.2.1. An educational agency or institution may disclose personally identifiable information from an education record of a student without consent if the disclosure is part of an agreement between organizations or subjects conducting studies for, or on behalf of, educational agencies or institutions to:
 - 2.2.1.1. Develop, validate, or administer predictive tests
 - 2.2.1.2. Administer student aid programs
 - 2.2.1.3. Improve instruction
 - 2.2.2. A school district or postsecondary institution that uses this exception is required to enter into a written agreement with the organization conducting the research that specifies:
 - 2.2.2.1. The determination of the exception
 - 2.2.2.2. The purpose, scope, and duration of the study
 - 2.2.2.3. The information to be disclosed
 - 2.2.2.4. That information from education records may only be used to meet the purposes of the study stated in the written agreement and must contain the current requirements in Department of Education regulations on redisclosure and destruction of information
 - 2.2.2.5. That the study will be conducted in a manner that does not permit personal identification of parents and students by anyone other than representatives of the Organization with legitimate interests
 - 2.2.2.6. That the Organization is required to destroy or return all personally identifiable information when no longer needed for the purposes of the study

- 2.2.2.7. The time period during which the Organization must either destroy or return the information
- 2.2.3. Education records may be released without consent under FERPA if all personally identifiable information has been removed including:
 - 2.2.3.1. Student's name and other direct personal identifiers, such as the student's social security number or student number
 - 2.2.3.2. Indirect identifiers, such as the name of the student's parent or other family members; the student's or family's address, and personal characteristics or other information that would make the student's identity easily traceable; and date and place of birth and mother's maiden name
 - 2.2.3.3. Biometric records, including one or more measurable biological or behavioral characteristics that can be used for automated
 - 2.2.3.4. recognition of an individual, including fingerprints, retina and iris patterns, voiceprints, DNA sequence, facial characteristics, and handwriting.
 - 2.2.3.5. Other information that, alone or in combination, is linked or linkable to a specific student that would allow a reasonable person in the school community, who does not have personal knowledge of the relevant circumstances, to identify the student with reasonable certainty.
- 2.3. For certain types of research directly funded by ED the Protection of Pupil Rights Amendment (PPRA) applies.
 - 2.3.1. PPRA prohibits students from being required, as part of any research project, to submit without prior consent to surveys, psychiatric examination, testing, or treatment, or psychological examination, testing, or treatment, in which the primary purpose is to reveal information concerning one or more of the following:
 - 2.3.1.1. Political affiliations or beliefs of the student or the student's parent
 - 2.3.1.2. Mental or psychological problems of the student or the student's family
 - 2.3.1.3. Sex behavior or attitudes
 - 2.3.1.4. Illegal, anti-social, self-incriminating, or demeaning behavior
 - 2.3.1.5. Critical appraisals of other individuals with whom respondents have close family relationships
 - 2.3.1.6. Legally recognized privileged or analogous relationships, such as those of lawyers, physicians, and ministers
 - 2.3.1.7. Religious practices, affiliations, or beliefs of the student or student's parent
 - 2.3.1.8. Income (other than that required by law to determine eligibility for participation in a program or for receiving financial assistance under such program

- 2.3.2. For certain types of research projects not directly funded by ED and conducted in a school that receives funding from ED: Policies and procedures include a process to verify compliance with ED regulations that schools are required to develop and adopt policies in conjunction with parents regarding the following:
 - 2.3.2.1. The right of a parent of a student to inspect, upon the request of the parent, a survey created by a third party before the survey is administered or distributed by a school to a student
 - 2.3.2.1.1. Any applicable procedures for granting a request by a parent for reasonable access to such survey within a reasonable period of time after the request is received
 - 2.3.2.2. Arrangements to protect student privacy that are provided by the agency in the event of the administration or distribution of a survey to a student containing one or more of the following items (including the right of a parent of a student to inspect, upon the request of the parent, any survey containing one or more of such items):
 - 2.3.2.2.1. Political affiliations or beliefs of the student or the student's parent
 - 2.3.2.2.2. Mental or psychological problems of the student or the student's family
 - 2.3.2.2.3. Sex behavior or attitudes
 - 2.3.2.2.4. Illegal, anti-social, self-incriminating, or demeaning behavior
 - 2.3.2.2.5. Critical appraisals of other individuals with whom respondents have close family relationships
 - 2.3.2.2.6. Legally recognized privileged or analogous relationships, such as those of lawyers, physicians, and ministers
 - 2.3.2.2.7. Religious practices, affiliations, or beliefs of the student or the student's parent
 - 2.3.2.2.8. Income (other than that required by law to determine eligibility for participation in a program or for receiving financial assistance under such program)
 - 2.3.2.3. The right of a parent of a student to inspect, upon the request of the parent, any instructional material used as part of the educational curriculum for the student
 - 2.3.2.3.1. Any applicable procedures for granting a request by a parent for reasonable access to instructional material received

- 2.3.2.4. The administration of physical examinations or screenings that the school or agency may administer to a student
- 2.3.2.5. The collection, disclosure, or use of personal information collected from students for the purpose of marketing or for selling that information (or otherwise providing that information to others for that purpose), including arrangements to protect student privacy that are provided by the agency in the event of such collection, disclosure, or use.
 - 2.3.2.5.1. The right of a parent of a student to inspect, upon the request of the parent, any instrument used in the collection of personal information before the instrument is administered or distributed to a student
 - 2.3.2.5.2. Any applicable procedures for granting a request by a parent for reasonable access to such instrument within a reasonable period of time after the request is received
- 2.4. Access to instructional material used in a research or experimentation program:
 - 2.4.1. All instructional material, including teachers' manuals, films, tapes, or other supplementary instructional material, which will be used in connection with any research or experimentation program or project must be available for inspection by the parents or guardians of the children engaged in such research.
- 2.5. Definitions:
 - 2.5.1. "Prior consent" means:
 - 2.5.1.1. Prior consent of the student, if the student is an adult or emancipated minor
 - 2.5.1.2. Prior written consent of the parent or guardian, if the student is not an emancipated minor
 - 2.5.2. "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.
 - 2.5.3. "Children" are persons enrolled in research not above the elementary or secondary education level, who have not reached the age of majority as determined under state law.
 - 2.5.4. "Psychiatric or psychological examination or test" means a method of obtaining information, including a group activity, that is not directly related to academic instruction and that is designed to elicit information about attitudes, habits, traits, opinions, beliefs or feelings (34 CFR §98.4)
 - 2.5.5. "Psychiatric or psychological treatment" means an activity involving the planned, systematic use of methods or techniques that are not directly related to academic instruction and that is designed to affect behavioral,

emotional, or attitudinal characteristics of an individual or group (34 CFR §98.4)

3. REFERENCES

- 3.1. 34 CFR §98
- 3.2. 34 CFR §99
- 3.3. 34 CFR §356

Appendix C.5: Additional Obligations – EPA

1. PURPOSE

- 1.1. This guidance outlines the additional obligations of investigators conducting research supported or conducted by EPA or whose results are intended to be submitted to EPA.

2. GUIDANCE

- 2.1. EPA regulates research that is conducted or supported by EPA.
- 2.2. EPA regulates research whose results are intended to be submitted to EPA, regardless of whether the research is conducted or supported by EPA or any federal agency.
- 2.3. “Research involving intentional exposure of a human subject” means a study of a substance in which the exposure to the substance experienced by a human subject participating in the study would not have occurred but for the human subject's participation in the study.
- 2.4. “Observational research” means any human research that is not research involving intentional exposure of a human subject.
- 2.5. Research involving the intentional exposure of pregnant women, nursing women, or children to any substance is prohibited.
- 2.6. Observational research involving children must meet the criteria in category (1) or (2) of “CHECKLIST: Research Involving Children (HRP-310)”
- 2.7. Observational research involving pregnant women must meet the criteria in “CHECKLIST: Pregnant Women (HRP-305).”
- 2.8. Research approved by the IRB must be submitted to the EPA human subjects research review official for final review and approval before the research can begin.

3. REFERENCES

- 3.1. 40 CFR §26
- 3.2. EPA Order 1000.17 Change A1

Appendix C.6: Additional Obligations – FDA

1. PURPOSE

- 1.1. This guidance outlines the additional obligations of investigators conducting FDA research as defined in “WORKSHEET: Human Research (HRP-421).

2. GUIDANCE

- 2.1. For all FDA-regulated research:

- 2.1.1. When a subject withdraws from a study:

- 2.1.1.1. The data collected on the subject to the point of withdrawal remains part of the study database and may not be removed.

- 2.1.1.1.1. The consent document cannot give the subject the option of having data removed.

- 2.1.1.2. You 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.

- 2.1.1.3. 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, you 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.

- 2.1.1.4. If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, you must not access for purposes related to the study the subject’s medical record or other confidential records requiring the subject’s consent.

- 2.1.1.4.1. You may review study data related to the participant collected prior to the subject’s withdrawal from the study, and may consult public records, such as those establishing survival status.

- 2.1.2. The Responsible Party for a clinical trial must register the trial and submit results information.

- 2.1.2.1. A principal investigator of a clinical trial is the Responsible Party if the clinical trial is investigator initiated or if so designated by a sponsor, grantee, contractor, or awardee.
- 2.1.2.2. Registration is required for the following trials:
 - 2.1.2.2.1. Controlled clinical investigations, other than phase 1 clinical investigations, of drugs or biological products
 - 2.1.2.2.2. Controlled trials with health outcomes of devices, other than small feasibility studies
 - 2.1.2.2.3. Pediatric post-market surveillance required by FDA
- 2.2. Requirements for studies conducted under an IND
 - 2.2.1. You, or any person acting on your behalf, cannot 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.
 - 2.2.1.1. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.
 - 2.2.2. You may not commercially distribute or test market an investigational new drug.
 - 2.2.3. Ensure that the 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 your care; and for the control of drugs under investigation.
 - 2.2.4. Obtain the informed consent of each human subject to whom the drug is administered, unless:
 - 2.2.4.1. Waived by the IRB for planned emergency research.
 - 2.2.4.2. Where the requirements in “WORKSHEET: Emergency Use - Drugs and Biologics (HRP-451)” are met
 - 2.2.5. Maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects.
 - 2.2.5.1. If the investigation is terminated, suspended, discontinued, or completed, return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies as directed by the sponsor.
 - 2.2.6. 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.
- 2.2.6.1. 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 chart(s), and the nurses' notes.
 - 2.2.6.2. The case history for each individual must document that informed consent was obtained prior to participation in the study.
- 2.2.7. Retain research records for the greater of:
- 2.2.7.1. Three years after completion of the research
 - 2.2.7.2. For drug studies conducted under an IND, two 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 two years after the investigation is discontinued and FDA is notified.
 - 2.2.7.3. For device studies conducted under an IDE or abbreviated IDE, two years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.
 - 2.2.7.4. The retention period requested by the sponsor.
- 2.2.8. Furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained.
- 2.2.9. Immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure.
- 2.2.9.1. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.
 - 2.2.9.2. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, immediately report the event to the sponsor.
 - 2.2.9.3. Record non-serious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol.
- 2.2.10. Provide the sponsor with an adequate report shortly after completion of your participation in the investigation.
- 2.2.11. Provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under part 54 of this chapter.

- 2.2.11.1. Promptly update this information if any relevant changes occur during the course of the investigation and for one year following the completion of the study.
 - 2.2.12. Assure that an IRB that complies with the requirements set forth in FDA regulations will be responsible for the initial and continuing review and approval of the proposed clinical study.
 - 2.2.12.1. Promptly report to the IRB all changes in the research activity and all **Unanticipated Problems Involving Risk to Subjects or Others**.
 - 2.2.12.2. Make no changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
 - 2.2.13. 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 of your records or reports.
 - 2.2.13.1. You are 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.
 - 2.2.14. If the investigational drug is subject to the Controlled Substances Act, 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.
- 2.3. Requirements for studies conducted under an abbreviated IDE
 - 2.3.1. You, or any person acting for or on behalf of you may not:
 - 2.3.1.1. Promote or test market the investigational device, until after FDA has approved the device for commercial distribution.
 - 2.3.1.2. Commercialize the investigational device by charging the subjects or investigators for a device a price larger than that necessary to recover costs of manufacture, research, development, and handling.
 - 2.3.1.3. Unduly prolong the investigation.
 - 2.3.1.4. Represent that the investigational device is safe or effective for the purposes for which it is being investigated.
 - 2.3.2. If the study is investigator-initiated:
 - 2.3.2.1. Label the device as follows:
 - 2.3.2.1.1. The device or its immediate package must bear a label with the following information: the name and place of business of the manufacturer, packer, or distributor (in accordance with §801.1), the

- quantity of contents, if appropriate, and the following statement: “CAUTION-Investigational device. Limited by Federal (or United States) law to investigational use.” The label or other labeling shall describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.
- 2.3.2.1.2. The device must not bear any statement that is false or misleading in any particular and shall not represent that the device is safe or effective for the purposes for which it is being investigated.
 - 2.3.2.2. Comply with the requirements of 21 CFR §812.46 with respect to monitoring investigations.
 - 2.3.2.3. Maintain the records required under 21 CFR §812.140(b) (4) and (5) and makes the reports required under 21 CFR §812.150(b) (1) through (3) and (5) through (10).
 - 2.3.2.4. Ensure that participating investigators maintain the records required by 21 CFR §812.140(a)(3)(i) and make the reports required under 21 CFR §812.150(a) (1), (2), (5), and (7).
 - 2.3.3. Ensure that the 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 your care, and for the control of devices under investigation.
 - 2.3.3.1. Ensure that informed consent is obtained in accordance with FDA regulations.
 - 2.3.4. You may determine whether potential subjects would be interested in participating in an investigation, but do not request the written informed consent of any subject to participate, and do not allow any subject to participate before obtaining IRB and FDA approval.
 - 2.3.5. Conduct the investigation in accordance with the signed agreement with the sponsor, the investigational plan, this part and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.
 - 2.3.6. Permit the investigational device to be used only with subjects under your supervision.
 - 2.3.6.1. Do not supply an investigational device to any person not authorized under this part to receive it.
 - 2.3.7. Disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required by FDA regulations.
 - 2.3.7.1. Promptly update this information if any relevant changes occur during the course of the investigation and for one year following completion of the study.

- 2.3.8. Upon completion or termination of a clinical investigation or your part of an investigation, or at the sponsor's request, return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.
- 2.3.9. Maintain the following accurate, complete, and current records relating to the your participation in an investigation:
 - 2.3.9.1. Records of each subject's case history and exposure to the device. Case histories include:
 - 2.3.9.1.1. 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 chart(s), and the nurses' notes
 - 2.3.9.1.2. Documents evidencing informed consent and, for any use of a device without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual must document that informed consent was obtained prior to participation in the study
 - 2.3.9.2. The protocol, with documents showing the dates of and reasons for each deviation from the protocol.
 - 2.3.9.3. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.
- 2.3.10. Permit authorized FDA employees, at reasonable times and in a reasonable manner:
 - 2.3.10.1. To enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept).
 - 2.3.10.2. To inspect and copy all records relating to an investigation.
 - 2.3.10.3. 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 you to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.
- 2.3.11. Prepare and submit the following complete, accurate, and timely reports:
 - 2.3.11.1. 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 you first learn of the effect.

- 2.3.11.2. Report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of your part of an investigation.
- 2.3.11.3. If you use a device without obtaining informed consent, report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.
- 2.3.11.4. Upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

2.4. Expanded Access

- 2.4.1. FDA has an expanded access program, which allows the use of investigational new drugs and approved drugs where availability is limited by a risk evaluation and mitigation strategy (REMS) when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition. The aim of expanded access is to facilitate the availability of such drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition.
- 2.4.2. In all cases of expanded access, investigators are responsible for reporting adverse drug events to the sponsor, ensuring that the informed consent requirements of part 50 of this chapter are met, ensuring that IRB review of the expanded access use is obtained in a manner consistent with the requirements of part 56 of this chapter, and maintaining accurate case histories and drug disposition records and retaining records in a manner consistent with the requirements of §312.62. Depending on the type of expanded access, other investigator responsibilities under subpart D may also apply.

2.5. Requirements for studies conducted under an IDE

- 2.5.1. You, or any person acting for or on behalf of you may not:
 - 2.5.1.1. Promote or test market the investigational device, until after FDA has approved the device for commercial distribution.
 - 2.5.1.2. Commercialize the investigational device by charging the subjects or investigators for a device a price larger than that necessary to recover costs of manufacture, research, development, and handling.
 - 2.5.1.3. Unduly prolong the investigation.
 - 2.5.1.4. Represent that the investigational device is safe or effective for the purposes for which it is being investigated.
- 2.5.2. Ensure that the 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 your care, and for the control of devices under investigation.

- 2.5.2.1. Ensure that informed consent is obtained in accordance with FDA regulations.
- 2.5.3. You may determine whether potential subjects would be interested in participating in an investigation, but do not request the written informed consent of any subject to participate, and do not allow any subject to participate before obtaining IRB and FDA approval.
- 2.5.4. Conduct the investigation in accordance with the signed agreement with the sponsor, the investigational plan, this part and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.
- 2.5.5. Permit the investigational device to be used only with subjects under your supervision.
 - 2.5.5.1. Do not supply an investigational device to any person not authorized under this part to receive it.
- 2.5.6. Disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required by FDA regulations.
 - 2.5.6.1. Promptly update this information if any relevant changes occur during the course of the investigation and for one year following completion of the study.
- 2.5.7. Upon completion or termination of a clinical investigation or your part of an investigation, or at the sponsor's request, return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.
- 2.5.8. Maintain the following accurate, complete, and current records relating to the your participation in an investigation:
 - 2.5.8.1. All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.
 - 2.5.8.2. Records of receipt, use or disposition of a device that relate to:
 - 2.5.8.2.1. The type and quantity of the device, the dates of its receipt, and the batch number or code mark
 - 2.5.8.2.2. The names of all persons who received, used, or disposed of each device
 - 2.5.8.2.3. Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of
 - 2.5.8.3. Records of each subject's case history and exposure to the device. Case histories include:
 - 2.5.8.3.1. 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 chart(s), and the nurses' notes.
- 2.5.8.3.2. Documents evidencing informed consent and, for any use of a device without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual must document that informed consent was obtained prior to participation in the study.
 - 2.5.8.3.3. 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.
 - 2.5.8.3.4. A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.
- 2.5.8.4. The protocol, with documents showing the dates of and reasons for each deviation from the protocol.
 - 2.5.8.5. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.
- 2.5.9. Permit authorized FDA employees, at reasonable times and in a reasonable manner:
- 2.5.9.1. To enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept).
 - 2.5.9.2. To inspect and copy all records relating to an investigation.
 - 2.5.9.3. 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 you to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.
- 2.5.10. Prepare and submit the following complete, accurate, and timely reports:
- 2.5.10.1. 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 you first learn of the effect.

- 2.5.10.2. Report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of your part of an investigation.
- 2.5.10.3. 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.
- 2.5.10.4. 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.
 - 2.5.10.4.1. Give such notice as soon as possible, but in no event later than 5 working days after the emergency occurred.
 - 2.5.10.4.2. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan.
 - 2.5.10.4.3. If these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, prior approval of FDA and the IRB are required.
- 2.5.10.5. If you use a device without obtaining informed consent, report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.
- 2.5.10.6. Within 3 months after termination or completion of the investigation or your part of the investigation, submit a final report to the sponsor and the reviewing IRB.
- 2.5.10.7. Upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

3. REFERENCES

- 3.1. 21 CFR §312.60, §312.61, §312.62, §312.64, §312.66, §312.68, §312.69, §312.300, §312.305, §812.40, §812.42, §812.43, §812.45, §812.46

Appendix C.7: Additional Obligations – ICH-GCP

1. PURPOSE

- 1.1. This guidance outlines the additional obligations of investigators conducting a **Clinical Trial**.

2. GUIDANCE

2.1. Investigator's Qualifications and Agreements

- 2.1.1. The investigator(s) 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 requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB, and/or the regulatory authority(ies).
- 2.1.2. 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 in other information sources provided by the sponsor.
- 2.1.3. The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.
- 2.1.4. The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).
- 2.1.5. The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

2.2. Adequate Resources

- 2.2.1. The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.
- 2.2.2. The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.
- 2.2.3. The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
- 2.2.4. The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

2.3. Medical Care of Trial Subjects

- 2.3.1. A qualified physician (or dentist, when appropriate), who is an investigator or a subinvestigator for the trial, should be responsible for all trial-related medical (or dental) decisions.
- 2.3.2. During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided

to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

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

2.4. Communication with IRB

- 2.4.1. Before initiating a trial, the investigator/institution should have written and dated approval from the IRB for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.
- 2.4.2. As part of the investigator's/institution's written application to the IRB, the investigator/institution should provide the IRB with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB.
- 2.4.3. During the trial the investigator/institution should provide to the IRB all documents subject to review.

2.5. Compliance with Protocol

- 2.5.1. The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval by the IRB. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.
- 2.5.2. The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval from the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).
- 2.5.3. The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.
- 2.5.4. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s)

should be submitted: a) to the IRB for review and approval, b) to the sponsor for agreement and, if required, c) to the regulatory authority(ies).

2.6. Investigational Product(s)

- 2.6.1. Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.
- 2.6.2. Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution..
- 2.6.3. The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(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 subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.
- 2.6.4. The investigational product(s) should be stored as specified by the sponsor and in accordance with applicable regulatory requirement(s).
- 2.6.5. The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.
- 2.6.6. The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

2.7. Randomization Procedures and Unblinding

- 2.7.1. The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

2.8. Informed Consent of Trial Subjects

- 2.8.1. In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB's written approval of the written informed consent form and any other written information to be provided to subjects.

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

information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

- 2.8.10. Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:
 - 2.8.10.1. That the trial involves research
 - 2.8.10.2. The purpose of the trial
 - 2.8.10.3. The trial treatment(s) and the probability for random assignment to each treatment
 - 2.8.10.4. The trial procedures to be followed, including all invasive procedures
 - 2.8.10.5. The subject's responsibilities
 - 2.8.10.6. Those aspects of the trial that are experimental
 - 2.8.10.7. The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant
 - 2.8.10.8. The reasonably expected benefits.
 - 2.8.10.8.1. When there is no intended clinical benefit to the subject, the subject should be made aware of this
 - 2.8.10.9. The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks
 - 2.8.10.10. The compensation and/or treatment available to the subject in the event of trial-related injury
 - 2.8.10.11. The anticipated prorated payment, if any, to the subject for participating in the trial
 - 2.8.10.12. The anticipated expenses, if any, to the subject for participating in the trial
 - 2.8.10.13. That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled
 - 2.8.10.14. That the monitor(s), the auditor(s), the IRB, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access
 - 2.8.10.15. That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available

- 2.8.10.16. If the results of the trial are published, the subject's identity will remain confidential. That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
- 2.8.10.17. The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
- 2.8.10.18. The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
- 2.8.10.19. The expected duration of the subject's participation in the trial.
- 2.8.10.20. The approximate number of subjects involved in the trial.
- 2.8.11. Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.
- 2.8.12. When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.
 - 2.8.12.1. Therapeutic trials (i.e. a trial in which there is anticipated direct clinical benefit to the subject) should be conducted in subjects who personally give consent and who sign and date the written informed consent form.
- 2.8.13. Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled: a) The objectives of the trial can not be met by means of a trial in subjects who can give informed consent personally. b) The foreseeable risks to the subjects are low. c) The negative impact on the subject's well-being is minimized and low. d) The trial is not prohibited by law. e) The approval of the IRB is expressly sought on the inclusion of such subjects, and the written approval covers this aspect. Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.
- 2.8.14. In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and

the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval by the IRB, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested.

2.9. Records and Reports

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

2.10. Progress Reports

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

2.11. Safety Reporting

- 2.11.1. All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB.
- 2.11.2. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.
- 2.11.3. For reported deaths, the investigator should supply the sponsor and the IRB with any additional requested information (e.g., autopsy reports and terminal medical reports).

2.12. Premature Termination or Suspension of a Trial

- 2.12.1. If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:
- 2.12.2. If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB, and should provide the sponsor and the IRB a detailed written explanation of the termination or suspension.
- 2.12.3. If the sponsor terminates or suspends a trial, the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB and provide the IRB a detailed written explanation of the termination or suspension.
- 2.12.4. 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 and provide the sponsor with a detailed written explanation of the termination or suspension.

2.13. Final Report(s) by Investigator

2.13.1. Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required.

2.14. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP).

3. REFERENCES

3.1. ICH Topic E 6 (R1) Guideline for Good Clinical Practice, (CPMP/ICH/135/95)