



## POLICY: Investigator Obligations

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### 1. PURPOSE

- 1.1. This guidance describes the obligations of investigators conducting <Human Research> overseen by Aspire IRB, CGIRB, MLIRB, NEIRB, or WIRB.
- 1.2. For research overseen by an IRB other than Aspire IRB, CGIRB, MLIRB, NEIRB, or WIRB, investigators should follow the requirements of that IRB.

### 2. POLICY

- 2.1. Investigators do not commence research until receipt of IRB approval and all other required approvals, such as radiation safety approval, biosafety approval, and approvals of departments or divisions that require approval of the use of their resources.
  - 2.1.1. If there are any questions about whether you are conducting research involving human subjects, contact the IRB before commencing the study.
- 2.2. Comply with all requirements and determinations of the IRB.
- 2.3. Ensure that there are adequate resources to carry out the research safely. This includes, but is not limited to, sufficient investigator time, appropriately qualified research team members, equipment, and space.
- 2.4. Ensure that research staff are qualified (e.g., including but not limited to appropriate training, education, expertise, credentials, protocol requirements and, when relevant, privileges) to perform procedures and duties assigned to them during the study.
- 2.5. Personally conduct or supervise the research.
- 2.6. Conduct the research in accordance with the relevant current protocol approved by the IRB.
- 2.7. Protect the rights, safety, and welfare of subjects involved in the research.
- 2.8. Submit proposed modifications to the IRB prior to their implementation.
  - 2.8.1. Do not make modifications to the research without prior IRB review and approval unless necessary to eliminate apparent immediate hazards to subjects.
- 2.9. Submit continuing reviews when requested by the IRB.
- 2.10. Submit a closure form to close research (end the IRB's oversight) when:
  - 2.10.1. The protocol is permanently closed to enrollment
  - 2.10.2. All subjects have completed all protocol related interventions and interactions
  - 2.10.3. For research subject to federal oversight other than FDA:
    - 2.10.3.1. No additional identifiable private information about the subjects is being obtained
    - 2.10.3.2. Your analysis of private identifiable information is completed
- 2.11. If research approval expires, stop all research activities and immediately contact the IRB.
- 2.12. Promptly report to the IRB the information items listed in "POLICY: Prompt Reporting Requirements (HRP-071)."
- 2.13. Do not accept or provide payments to professionals in exchange for referrals of potential subjects ("finder's fees.")
- 2.14. Do not accept payments designed to accelerate recruitment that were tied to the rate or timing of enrollment ("bonus payments") without prior IRB approval.
- 2.15. For studies regulated by a federal department or agency, follow the additional obligations, as applicable:
  - 2.15.1. "INVESTIGATOR GUIDANCE: Additional DOD Obligations (HRP-810)"
  - 2.15.2. "INVESTIGATOR GUIDANCE: Additional DOE Obligations (HRP-811)"
  - 2.15.3. "INVESTIGATOR GUIDANCE: Additional DOJ Obligations (HRP-812)"
  - 2.15.4. "INVESTIGATOR GUIDANCE: Additional EPA Obligations (HRP-813)"
  - 2.15.5. "INVESTIGATOR GUIDANCE: Additional ED Obligations (HRP-814)"
  - 2.15.6. "INVESTIGATOR GUIDANCE: Additional FDA Obligations (HRP-815)"



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- 2.16. For studies where ICH-GCP compliance is required, follow additional the obligations in “INVESTIGATOR GUIDANCE: Additional ICH-GCP Obligations (HRP-816).”
- 2.17. When required by the IRB ensure that consent, permission, and assent are obtained and documented in accordance with the relevant current protocol as approved by the IRB.
- 2.18. Retain research records (including signed consent documents) for the greater of:
  - 2.18.1. Three years after completion of the research
  - 2.18.2. 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.
  - 2.18.3. 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.
  - 2.18.4. The retention period required by the sponsor
  - 2.18.5. The retention period required by local, state, or international law.
    - 2.18.5.1. HIPAA requires signed authorizations to be retained for six years from the date signed or the date when it last was in effect, whichever is later.
  - 2.18.6. The retention period required by a site that is not part of this [Organization].

### 3. REFERENCES

- 3.1. 21 CFR §50, §56
- 3.2. 45 CFR §46

### 4. REVISION HISTORY

- 4.1. **Edition 2.3:** Change identifier from HRP-800 to HRP-070 to categorize as a Policy, update reference of “HRP-801” to “HRP-071”, and minor wording revision to 2.1.

## POLICY: Prompt Reporting Requirements

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### 1. PURPOSE

- 1.1. This guidance describes the information that investigators must promptly report to the IRB when the research is subject to oversight by Aspire IRB, CGIRB, MLIRB, NEIRB, or WIRB.
- 1.2. For research overseen by an IRB other than Aspire IRB, CGIRB, MLIRB, NEIRB, or WIRB, investigators should follow the requirements of that IRB.

### 2. POLICY

- 2.1. Investigators are to report the following information items to the IRB within 5 days:
  - 2.1.1. New or increased risk<sup>1</sup>
  - 2.1.2. Protocol deviation that harmed a subject or placed subject at risk of harm
  - 2.1.3. Protocol deviation made without prior IRB approval to eliminate an immediate hazard to a subject
  - 2.1.4. Audit, inspection, or inquiry by a federal agency
  - 2.1.5. Written reports of federal agencies (e.g., FDA Form 483)
  - 2.1.6. <Allegation of Noncompliance> or <Finding of Noncompliance>
  - 2.1.7. Unauthorized disclosure of confidential information
  - 2.1.8. Unresolved subject complaint
  - 2.1.9. Suspension or premature termination by the sponsor, investigator, or institution
  - 2.1.10. Incarceration of a subject in a research study not approved to involve prisoners
  - 2.1.11. Adverse events or IND safety reports that require a change to the protocol or consent
  - 2.1.12. State medical board actions
  - 2.1.13. Unanticipated adverse device effect<sup>2</sup>
  - 2.1.14. Information where the sponsor requires prompt reporting to the IRB
- 2.2. Information not listed above does not require prompt reporting to Aspire IRB, CGIRB, MLIRB, NEIRB, or WIRB.

### 3. REFERENCES

- 3.1. 21 CFR §56.108(b)
- 3.2. 45 CFR §46.103(b)(5)

### 4. REVISION HISTORY

- 4.1. **Edition 1.3:** Change identifier from HRP-801 to HRP-071 to categorize as a Policy and minor wording revision to 2.1.

<sup>1</sup> For example, publications indicating a new risk, new risk in an investigator brochure, FDA black box warning, new risk identified in a data safety monitoring report, information or change that adversely affects subject safety, or information or change that adversely affects the conduct of the research.

<sup>2</sup> Unanticipated adverse device effect means 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.

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### 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 State or local 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
- 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 use 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 form and any other information

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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



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- 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
- 4.2. 45 CFR §46.116

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| <b>INVESTIGATOR GUIDANCE:<br/>Documentation of Informed Consent</b> |                     |                        |                    |
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## 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 form 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.

## 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:



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- 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>
- 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>
- 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



# INVESTIGATOR GUIDANCE: Additional DOD Obligations

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## 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.

### 2.3. Administrative Review

- 2.3.1. The DOD Component must conduct an appropriate administrative review of the research involving human subjects. The DOD Component administrative review must be conducted before the research involving human subjects can begin, to ensure compliance with all applicable regulations and policies, including any applicable laws and requirements and cultural sensitivities of a foreign country when the research is conducted in a foreign country.
  - 2.3.1.1. DOD institutions collaborating with non-DOD institutions may rely on a collaborating non-DOD institution's IRB if the following conditions are met:
    - 2.3.1.2. Each institution engaged in non-exempt human participant research must have a current federal assurance of compliance.
    - 2.3.1.3. The involvement of DOD personnel in the conduct of the research is secondary to that of the non- DOD institution.
    - 2.3.1.4. The DOD institution, non-DOD institution, and the non-DOD institution's IRB have a written agreement defining the responsibilities and authorities of each organization in complying with all legal requirements. This agreement must be approved by the DOD component prior to the DOD institution's engagement in the research.
  - 2.3.2. For DOD-supported non-exempt research involving human participants involving classified information reviewed by a non-DOD IRB, 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 participants during the consent process; and information provided by human participants during the course of the research.

### 2.4. International Research

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- 2.4.1. You or the organization must obtain permission to conduct research in that country by certification or local ethics review.
- 2.4.2. You must follow all local laws, regulations, customs, and practices.
- 2.5. Reporting: The following findings in DOD-supported research must be reported to the DOD human research protection officer within 30 days:
  - 2.5.1. Determinations of <Serious Noncompliance> or <Continuing Noncompliance>
  - 2.5.2. Significant changes to the research protocol that are approved by the IRB
  - 2.5.3. The results of the IRB continuing review
  - 2.5.4. Change of reviewing IRB
  - 2.5.5. 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
  - 2.5.6. <Unanticipated Problems Involving Risk to Subjects or Others>
  - 2.5.7. <Suspension of IRB approval>
  - 2.5.8. <Termination of IRB approval>
- 2.6. Survey Approval
  - 2.6.1. 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.
- 2.7. Multisite Research
  - 2.7.1. When conducting multi-site research, a formal agreement between organizations is required to specify the roles and responsibilities of each party.
- 2.8. Definition of <Minimal Risk>
  - 2.8.1. 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).
  - 2.8.2. The organization applies this definition to all research regardless of funding.
- 2.9. Appointment of a Research Monitor:
  - 2.9.1. This is required for research involving greater than minimal risk.
  - 2.9.2. 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.
  - 2.9.3. The research monitor is appointed by name and must be independent of the team conducting the research.
  - 2.9.4. There may be more than one research monitor (e.g. if different skills or experience are needed).
  - 2.9.5. 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.
  - 2.9.6. The IRB or institutional official must communicate with research monitors to confirm their duties, authorities, and responsibilities.
  - 2.9.7. The duties of the research monitor are determined on the basis of specific risks or concerns about the research.
    - 2.9.7.1. The research monitor may perform oversight functions (e.g., observe recruitment, enrollment procedures, and the consent process,

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oversee study interventions and interactions, review monitoring plans and <Unanticipated Problems Involving Risk to Subjects or Others>, oversee data matching, data collection and analysis).

- 2.9.7.2. The research monitor may discuss the research protocol with investigators, interview human subjects, and consult with others outside of the study.
- 2.9.7.3. Report observations and findings to the IRB or a designated official.
- 2.9.8. The research monitor has the authority to:
  - 2.9.8.1. Stop a research study in progress.
  - 2.9.8.2. Remove individuals from study.
  - 2.9.8.3. Take any steps to protect the safety and well-being of subjects until the IRB can assess.
- 2.9.9. Recruitment of Service Members
  - 2.9.9.1. Superiors of service members are not permitted to influence the decision of their subordinates.
  - 2.9.9.2. Superiors of service members in the chain of command may not be present at the time of recruitment.
  - 2.9.9.3. Officers and senior non-commissioned officers have a separate opportunity to participate.
- 2.9.10. When recruitment involves group setting, the IRB may require that an independent ombudsman is present.
- 2.9.11. Compensation of Service Members:
  - 2.9.11.1. Service member may not receive pay or compensation for research during duty hours.
  - 2.9.11.2. A service member may be compensated for research if the subject is involved in the research when not on duty.
  - 2.9.11.3. Federal employees while on duty and non-Federal persons may be compensated for blood draws for research up to \$50 for each blood draw.
  - 2.9.11.4. 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.
- 2.10. Consent
  - 2.10.1. The disclosure for research-related injury must follow the requirements of the DOD component.
  - 2.10.2. If the subject undergoes interactions or interventions for the primary purpose of obtaining data regarding the effect of the intervention or interaction, the subject is considered an “experimental subject.” Research involving experimental subjects as defined in DODI 3216.02 is a subset of research involving human subjects. For experimental subjects:
    - 2.10.2.1. A waiver of the consent process is prohibited unless a waiver is obtained from the Assistant Secretary of DOD for Research and Engineering.
    - 2.10.2.2. The Assistant Secretary for DOD for Research and Engineering may waive the requirements for consent when all of the following are met:
      - 2.10.2.2.1. The research is necessary to advance the development of a medical product for the Military Services.
      - 2.10.2.2.2. The research may directly benefit the individual experimental subject.

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- 2.10.2.2.3. The research is conducted in compliance with all other applicable laws and regulations.
- 2.10.2.3. The IRB may waive the consent process for subjects who are not “experimental subjects.”
- 2.10.2.4. If consent is to be obtained from the experimental subjects’ legal representative, the research must intend to benefit the individual subject.
  - 2.10.2.4.1. The determination that research is intended to be beneficial to the individual experimental subject must be made by an IRB.
- 2.10.3. Waivers of consent are prohibited for classified research.
- 2.11. Research on Pregnant Women
  - 2.11.1. Research involving pregnant women and fetuses as subjects is subject to HHS Subpart B except:
    - 2.11.1.1. The phrase “biomedical knowledge” is replaced with “generalizable knowledge.”
    - 2.11.1.2. 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.
- 2.12. Research on Prisoners
  - 2.12.1. Research involving prisoners is subject to HHS Subparts C.
  - 2.12.2. Research involving prisoners cannot be reviewed by the expedited procedure.
  - 2.12.3. When the IRB reviews research involving prisoners, at least one prisoner representative must be present for quorum. The prisoner representative may be a prisoner, an employee of the prison, or an individual not affiliated with the prison.
  - 2.12.4. In addition to allowable categories of research on prisoners in Subpart C, epidemiological research is also allowable when:
    - 2.12.4.1. The research describes the prevalence or incidence of a disease by identifying all cases or studies potential risk factor association for a disease.
    - 2.12.4.2. The research presents no more than minimal risk.
    - 2.12.4.3. The research presents no more than an inconvenience to the subject.
  - 2.12.5. 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

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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.

2.12.6. Research involving a detainee as a human subject is prohibited.

2.12.6.1. 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.

2.12.7. Research involving prisoners of war is prohibited.

2.12.7.1. "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.

2.12.7.2. 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.

2.13. Research on Children

2.13.1. Research involving children is subject to the HHS Subpart D.

2.13.2. 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.

2.14. Research on Fetal Tissue

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

2.15. Waiver of Informed consent for Planned Emergency Research

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

2.16. Records

2.16.1. 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.

2.17. Non-exempt Classified Research

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- 2.17.1. 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.
- 2.17.2. Secretary of DOD approval is required for all classified non-exempt research involving subjects.
  - 2.17.2.1. 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.
- 2.17.3. Waivers of informed consent are prohibited.
- 2.17.4. Informed consent procedures must include:
  - 2.17.4.1. 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.
  - 2.17.4.2. A statement that the research involving human subjects is classified and an explanation of the impact of the classification.
- 2.17.5. IRB approval process must meet the following requirements:
  - 2.17.5.1. IRB review must be conducted using a full board review. Use of an expedited review procedure is prohibited.
  - 2.17.5.2. 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).
  - 2.17.5.3. 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.
  - 2.17.5.4. The IRB must determine whether potential subjects need access to classified information to make a valid, informed consent decision.
- 2.17.6. 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

### 4. REVISION HISTORY

- 4.1. **Edition 003:** Move information about civilian researchers, add information about surveys across DOD components, change references to officers and non-commissions officers to superiors of service members, add reference to recruitment in a group setting.
- 4.2. **Edition 002:** Updates based on revised guidance

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### 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

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- 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. Requirements for human subject protections for classified research apply to all research conducted or supported by the DOE, including contracts, and including Human Terrain Mapping research.
  - 2.3. Requirements for human subject protections and their accompanying Contractor Requirements Documents (CRDs) apply to all research conducted at DOE institutions regardless of funding source, or by DOE employees/contractor personnel regardless of funding source or location conducted, and whether done domestically or in an international environment, and including Human Terrain Mapping research.
  - 2.4. DOE worker are considered vulnerable subjects and shall be afforded additional protections as determined by the IRB.
  - 2.5. The DOE Institutional Official is responsible for
    - 2.5.1. Ensuring the Central DOE Review Board and the Central DOE Institutional Review Board- Classified comply with applicable requirements.
    - 2.5.2. Formally appointing the chair, vice-chair, and other IRB members.
    - 2.5.3. Approving classified research conducted with DOE funding at its sites/laboratories and by its employees and contractors after IRB approval and prior to initiation.
  - 2.6. No human participant research conducted with DOE funding at DOE institutions (Headquarters or sites/laboratories, regardless of funding source), or by DOE employees and contractor personnel (regardless of funding source or location conducted), and whether done domestically or in an international environment, including classified and proprietary research, shall be initiated without both a Federalwide Assurance and approval by the cognizant IRB in accordance with 10 CFR Part 745.103.
  - 2.7. The DOE Human Subjects Protection Program Manager is responsible for:
  - 2.8. Developing procedures for the classified research program in consultation with the National Nuclear Security Administration Human Subject Protection Program Manager.
    - 2.8.1. Conducting biennial performance reviews of all IRBs that review classified research involving human participants to assess compliance, in consultation with the National Nuclear Security Administration human participant protection program manager.
    - 2.8.2. Reviewing and approving local plans to correct noncompliance or mitigate adverse events and unanticipated problems involving risks to participants or others.
    - 2.8.3. Reviewing and approving statements of work for classified Human Terrain Mapping projects submitted by DOE's non-National Nuclear Security Administration sites or projects.
    - 2.8.4. Making recommendations to the Secretary after concurrence from the organizational Official, on a project by project basis, regarding exemptions from the requirements for classified research.
    - 2.8.5. Concurs on human participant provisions for classified research in interagency agreements, in consultation with the National Nuclear Security Administration, as appropriate.
    - 2.8.6. Maintaining an unclassified list of classified projects.
  - 2.9. Within 48 hours of the following (or immediately 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:
    - 2.9.1. Any significant adverse events, unanticipated problems, and complaints about the research,



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- 2.9.2. Any <Suspension of IRB Approval> <Termination of IRB Approval>;
- 2.9.3. 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
- 2.10. When conducting classified research, the use of exemptions is prohibited. The fact that research meets a particular exemption category may be noted, but review by a convened IRB is required.
- 2.11. When conducting classified research, the use of the expedited review procedure is prohibited.
- 2.12. Research involving human subjects must also comply with Federal and DOE-specific requirements for protecting the personally identifiable information (PII) generated in such research. Methods for protecting such data must be specified in the application.
- 2.13. Requirements include:
  - 2.13.1. Keeping PII confidential
  - 2.13.2. Releasing PII only under a procedure approved by the responsible IRB and DOE
  - 2.13.3. Using PII only for purposes of the IRB-approved project
  - 2.13.4. Handling and marking documents containing PII as "containing PII or containing Protected Health Information (PHI)"
  - 2.13.5. Establishing and documenting safeguards to prevent unauthorized use or disclosure of PII and PHI
  - 2.13.6. Protecting PII stored on removable media using encryption procedures that are compliant with Federal standards (FIPS-140-2 certified)
  - 2.13.7. Sending removable media containing PII by express overnight service with signature and tracking capability
  - 2.13.8. Sending passwords to encrypted files separately from the files
  - 2.13.9. And using 2-factor authentication for log-on access for remote systems.
- 2.14. Suspected loss of PII or PHI must be reported immediately to: 1) the DOE funding office Program Manager, or, if funded by an outside organization, the Program Manager at that organization; 2) the applicable DOE site or central IRB. If the DOE Program Manager and/or IRB is unreachable, the PI is responsible for immediately notifying the DOE Joint Cybersecurity Coordination Center (JC3) (1-866-941-2472).
- 2.15. When conducting classified research,
  - 2.15.1. consent documents must disclose:
    - 2.15.1.1. The identity of the sponsoring agency, unless the sponsor requests that it not be done, because doing so could compromise intelligence sources or methods; the research involves no more than minimal risk to participants; and the IRB determines that by not disclosing the identity, the investigators will not adversely affect the participants.
    - 2.15.1.2. Consent documents will state the project is classified, and what it means for the purposes of the research project
    - 2.15.1.3. The IRB must determine if participants need access to classified information to make a valid consent decision.
  - 2.15.2. The IRB may not grant a waiver of the consent process or waiver of documentation of consent.

### 3. REFERENCES

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



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### 4. REVISION HISTORY

4.1. **Edition 003:** Updates based on revised guidance

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## 1. PURPOSE

1.1. This guidance outlines the additional obligations of investigators conducting DOJ research.

## 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 does not have to 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.

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- 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.

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- 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.



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- 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

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### 1. PURPOSE

- 1.1. This guidance outlines the additional obligations of investigators conducting ED research.

### 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

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- 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

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- 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.



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- 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



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### 1. PURPOSE

- 1.1. This guidance outlines the additional obligations of investigators conducting EPA research.

### 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

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### 1. PURPOSE

1.1. This guidance outlines the additional obligations of investigators conducting FDA research.

### 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

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- 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.

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- 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.

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- 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.

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- 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

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- 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.

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- 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.

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- 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

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### 1. PURPOSE

- 1.1. This guidance outlines the additional obligations of investigators conducting research subject to ICH-GCP.

### 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

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- 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

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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

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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

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- 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.

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- 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

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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)