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## 1. PURPOSE

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

## 2. GUIDANCE

- 2.1. For all FDA-regulated research:

- 2.1.1. When a subject withdraws from a study:

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

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

2.1.1.2. You may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.

2.1.1.3. If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information as described in the previous bullet, you must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). IRB approval of informed consent documents is required.

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

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

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

2.1.2.1. A principal investigator of a clinical trial is the Responsible Party if the clinical trial is investigator initiated or if so designated by a sponsor, grantee, contractor, or awardee.

2.1.2.2. Registration is required for the following trials:

2.1.2.2.1. Controlled clinical investigations, other than phase 1 clinical investigations, of drugs or biological products

2.1.2.2.2. Controlled trials with health outcomes of devices, other than small feasibility studies

2.1.2.2.3. Pediatric post-market surveillance required by FDA

- 2.2. Requirements for studies conducted under an IND

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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