

RESEARCH INVOLVING MEDICAL DEVICES

1. Overview

Investigators and IRBs must ensure that research (i.e., clinical investigation) involving medical devices is conducted in accordance with applicable federal regulations. These regulations describe, among other things, requirements for Investigational Device Exemptions (IDEs), use of custom devices and humanitarian use devices (HUDs), investigational device accountability and record retention, and responsibilities of investigators, IRBs, and sponsors when research is conducted with medical devices.

The purpose of this policy is to describe the requirements for research involving medical devices, including the responsibilities of investigators, IRBs, and sponsors.

2. Definitions

Clinical Investigation: Also: **research, clinical research, clinical study.** Any experiment that involves a test article and one or more human subjects that either:

- Meets the requirements for prior submission to the FDA under sections 505(i) or 520(g) of the Food, Drug, and Cosmetic Act; or
- Need not meet the requirements for prior submission to the FDA under the sections noted above, but the results of which are intended to be later submitted to or held for inspection by the FDA as part of an application for a research or marketing permit.

Note: Non-clinical laboratory studies are not considered to be clinical investigations. See the DHHS definition of research for DHHS-regulated research.

Device: Also: **medical device.** Instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article (including a component part), or accessory that is recognized in the official National Formulary or United States Pharmacopoeia (or any supplement to these) and is:

- Intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease in man or other animals, or
- Intended to affect the structure or any function of the body of man or other animals, that does not achieve any of its primary intended purposes through chemical action within or on the body, and is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

Implant: A device that is placed into a surgically or naturally formed cavity of the human body if it is intended to remain there for a period of 30 days or more.

Investigational Device: A device (including a transitional device) that is the object of an investigation.

Investigational Device Exemption (IDE): An application that permits a device that would otherwise be required to comply with a performance standard (*i.e.*, 510(k) submission) or to have pre-market approval by FDA to be legally shipped for a clinical investigation.

Non-Significant Risk (NSR) Device: An investigational device that does not meet the definition of a significant risk device.

Significant Risk (SR) Device: An investigational device that is:

- Intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- For use in supporting or sustaining human life and represents a potential for serious risk to the health, safety, or welfare of a subject;
- For a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
- Otherwise presents a potential for serious risk to a subject.

Custom Device: A device that necessarily deviates from devices generally available or from an applicable performance standard or pre-market approval requirement to comply with the order of an individual physician or dentist and that is:

- Not generally available or generally used by other physicians or dentists;
- Not generally available in finished form for purchase or for dispensing upon prescription;
- Not offered for commercial distribution through labeling or advertising; and
- Intended for use by an individual patient named in the order of a physician or dentist and is to be made in a specific form for that patient, or is intended to meet the special needs of the physician or dentist in the course of professional practice.

Humanitarian Device Exemption (HDE): An application that permits the marketing of a humanitarian use device.

Humanitarian Use Device (HUD): A device that is intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect (or are manifested in) fewer than 4000 individuals in the US per year.

Sponsor-Investigator: An individual who initiates (*i.e.*, obtains an IND or IDE) and conducts an investigation and under whose immediate direction an investigational drug or device is administered, dispensed, or used. *Note: The regulatory requirements applicable to a sponsor-investigator include those applicable to both an investigator and a sponsor.*

Transitional Device: A device subject to section 520(l) of the Food, Drug, and Cosmetic Act; a device that FDA considered to be a new drug or an antibiotic drug before May 28, 1976.

3. General Information

- A. When human subjects research involves the use of medical devices, FDA regulations apply. Investigators must provide sufficient information about the device for the IRB to evaluate its associated risks and benefits, including the FDA approval status of the product (i.e., approved/cleared for marketing or investigational).
- B. Medical devices can receive FDA approval or clearance for marketing in several different ways. Examples include pre-market approval, which is given following clinical trials to determine the safety and efficacy of a new device, and marketing clearance (510(k) pre-market notification), granted by FDA when a device is determined to be “substantially equivalent” to a device already on the market. Investigational devices include medical devices under clinical investigation to test their safety and efficacy, as well as investigation of certain modifications or new intended uses of already marketed devices.
- C. The FDA requirements for studies involving investigational devices are proportional to the potential risk level (see “Significant and Non-Significant Risk Device Studies” below). Studies presenting a significant risk to participants must be conducted under an IDE. Non-significant risk studies do not require an IDE, but must meet the abbreviated IDE requirements described in Attachment 2. Certain investigational device studies are exempt from the IDE requirements. For information about the FDA exemptions from the IDE requirements, see Attachment 1.
- D. When an IDE is required for the proposed use of an investigational device in research, investigators must submit an application to FDA. (Note: There are no pre-printed application forms.) An IDE application must contain certain information, including the submission cover sheet ([Form FDA 3514](#)), study’s investigational plan (i.e., protocol), report of prior investigations, description of the device’s manufacturing and labeling, and copies of investigator agreements, informed consent documents, and other information to be provided to research participants. An IDE number will be assigned by FDA upon receipt of the application. Unless earlier notification is received, studies may be initiated 30 days after FDA’s receipt of the IDE. Final IRB approval will not be given until a valid IDE number is provided. For more information about obtaining an IDE, see [21 CFR 812 Subpart B - Application and Administrative Action](#) and [Device Advice: IDE Application](#).
- E. An investigator obtaining an IDE for the proposed use of an investigational device in research becomes a “sponsor-investigator,” and additional institutional requirements apply to assist investigators in complying with applicable FDA regulations (see “Additional Responsibilities of Sponsor-Investigators” below).
- F. FDA regulations allow sponsors to charge for an investigational device. The charge should not exceed an amount “necessary to recover the costs of manufacture, research, development, and handling of the investigational device.” Proposed charges are included

in the IDE application. The IRBs should ensure that charges for investigational devices appear appropriate and equitable and that any additional costs to participants are disclosed during the consent process.

- G. The “off-label” use of a marketed device (i.e., a use other than the indication(s) approved by FDA) by a physician for treatment purposes does not require an IDE or IRB approval. When such uses meet the regulatory definitions of *research* or *clinical investigation*, IRB approval is required. An IDE may also be required, unless the study meets the conditions for an abbreviated IDE (described in Attachment 2) or exemption (described in Attachment 1).
- H. Additional requirements apply to the emergency use of an investigational device and planned emergency research involving investigational devices subject to FDA regulations. For more information, see OSU HRPP policies [[Emergency Use of Investigational Drugs, Biologics, or Devices](#)] and [[Planned Emergency Research](#)].
- I. In certain situations, an investigational device intended to treat a serious or immediately life-threatening condition may be used under a Treatment IDE. Such “treatment use” of an investigational device requires IRB review and approval. For more information, see [21 CFR 812.36 - Treatment Use of an Investigational Device](#), [Device Advice: IDE Early/Expanded Access](#), or contact ORRP.
- J. The “compassionate use” of an investigational device allows access for a patient (or small group of patients) who does not meet the requirements for inclusion in a study of the device, but for whom a physician believes the device may provide benefit in treating and/or diagnosing the disease or condition. Such use of an investigational device is considered a protocol “deviation” for which prior FDA approval and reporting to the IRB is required. For more information, see FDA guidance [Device Advice: IDE Early/Expanded Access](#) and OSU HRPP policy [[Event Reporting – Unanticipated Problems Involving Risks to Subjects or Others, Adverse Events, and Other Problems](#)].
- K. Although custom devices and humanitarian use devices are not investigational, additional FDA requirements apply to their use, including IRB notification or review as described below (see “Custom Devices” and “Humanitarian Use Devices”).

4. Submission and Pre-Review Procedures

- A. To describe proposed uses of medical devices in human subjects research, investigators will submit *Appendix E: Devices* with the *Initial Review of Human Subjects Research* application form and all applicable attachments. For more information about IRB submission requirements, see OSU HRPP policy [[IRB Submission and Pre-Review](#)].
- B. During the pre-review process, ORRP IRB Protocol Analysts are responsible for making an initial determination about the FDA requirements applicable to the device’s use. For investigational devices, one of the following determinations will be made:

- The device requires an IDE (i.e., significant risk device study)
- The device fulfills the requirements for an abbreviated IDE (i.e., non-significant risk device study)
- The device meets one of the FDA exemptions from the IDE requirements.

The IRBs will make the final determination. Note: For assistance in determining whether an IDE is required in a specific situation, the FDA may be contacted directly. (For contact information, see FDA guidance ["Off-label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices.](#))

- C. When the research involves a device with an IDE, ORRP IRB Protocol Analysts will verify that the IDE number provided by the investigator is valid. Protocol-specific confirmation (e.g., sponsor's protocol cover sheet, FDA or sponsor correspondence, etc.) will be obtained.

5. IRB Review Requirements

- A. In general, the convened IRBs will review proposed research involving investigational devices considering the criteria for approval as described by regulations and OSU HRPP policy [[Review of Research by the Convened IRB](#)]. Note: Research involving a device for which an IDE is required is not eligible for expedited review.
- B. When research involves the use of an investigational device, to approve the research the IRBs will also require the following:
- Available clinical and non-clinical information on the investigational product that is adequate to support the proposed research and to make the SR/NSR determination (when applicable)
 - A valid IDE, unless the proposed use of the device fulfills the requirements for an abbreviated IDE (non-significant risk device) or meets one of the FDA exemptions from the IDE requirements
 - An adequate plan for monitoring data to ensure the safety of participants and for reporting adverse events (unanticipated adverse device effects) and unanticipated problems involving risks to participants or others
 - A plan for control, accountability, and storage of the investigational device that ensures that the product will be used only in the approved research under the direction of the approved investigator(s)
 - For sponsor-investigators, that they are knowledgeable about and will comply with the additional FDA requirements associated with conducting research for which an IDE has been obtained.

6. Significant and Non-Significant Risk Device Studies

- A. Significant risk device studies pose the potential for serious risk to the health, safety, and/or welfare of research participants. Examples include studies involving surgical

sutures, cardiac pacemakers, intravascular stents, and orthopedic implants. An IDE is required for SR device studies.

- B. Non-significant risk device studies do not present potential serious risks to participants. Examples include studies involving most daily-wear contact lenses and lens solutions, ultrasonic dental scalers, and foley catheters. NSR studies do not require an IDE, but must follow the abbreviated IDE requirements (see Attachment 2).
- C. Sponsors are responsible for making the initial risk determination for a proposed investigational device study. The IRB must review the sponsor's SR or NSR assessment and may modify the determination if the IRB disagrees. If the FDA has made the SR or NSR determination prior to IRB review, the IRB is not required to make this determination; FDA's determination is final. Note: FDA makes SR/NSR determinations when an IDE is submitted, or if asked by a sponsor, investigator, or IRB and will provide documentation of its decision upon request.
- D. The IRB will make the SR or NSR determination for a study by convened review. A description of the device, reports of prior studies conducted with the device, proposed investigational plan, risk assessment, and subject selection criteria should be considered. The sponsor's rationale for its SR or NSR determination (unless already determined by FDA) should also be reviewed. The SR/NSR determination must be documented in the IRB minutes, including a description of the reason(s) for the Board's decision.
- E. The IRB is not required to make a SR/NSR determination for studies involving devices that meet the criteria for exemption from the IDE regulations.
- F. For examples of significant risk and non-significant risk devices, see FDA guidance [Significant Risk and Nonsignificant Risk Medical Device Studies](#). Note: Because the device's proposed use in a study must be reviewed, inclusion of a device on either list should not be the only consideration used by the IRB in making the SR/NSR determination.

7. Investigational Device Control, Accountability, and Record Retention

- A. Investigational devices used in OSU research must be appropriately controlled and stored in compliance with IRB and FDA requirements and applicable OSU policies. Such requirements include processes to ensure that investigational products are manufactured, handled, and stored in compliance with applicable good manufacturing practices; inventory and accountability records are maintained for investigational device receipt, dispensing, and disposition; and investigational devices are used only in accordance with available information regarding their design, physical and chemical composition, performance, safety, biocompatibility, labeling, and the approved protocol.
- B. Investigators must provide a plan to ensure that investigational devices will be used according to the IRB-approved protocol, under the direction of the approved

investigator(s), and in compliance with FDA and OSU requirements. For more information describing the responsibilities of investigators conducting research with investigational devices, see Attachment 3.

8. Additional Responsibilities of Sponsor-Investigators

- A. Investigators obtaining an IDE to initiate and conduct research must also fulfill the federal requirements of sponsors. These requirements include (but are not limited to) additional FDA reporting (e.g., annual progress reports), data monitoring, and recordkeeping obligations. Institutional requirements for “sponsor-investigators” conducting research with investigational devices also apply, as described below.
- B. When an OSU investigator obtains an IDE to perform human subjects research, a representative from the College of Medicine Office of Research (COM/OR) will meet with the PI (and research staff, as applicable) to review the FDA responsibilities of investigators and sponsors. The COM/OR works with the IRBs and Office of Research Compliance to assure investigator and institutional compliance with IRB and FDA requirements. The COM/OR will assist investigators with information on FDA requirements, submission of required FDA reporting, and device accountability and recordkeeping procedures.
- C. College of Medicine Office of Research review is required for first-time IDE holders performing human subjects research (regardless of College/Department affiliation). Experienced sponsor-investigators will not require COM/OR review, at the discretion of the IRB. Final IRB approval will not be given until documentation of COM/OR review (as applicable) is provided.
- D. In addition to FDA regulations for the protection of human subjects (21 CFR Parts 50, and 56) and use of investigational devices (21 CFR 812), additional regulations may apply to sponsor-investigators, depending on the nature of the research. These regulations include:
- [Electronic Records; Electronic Signatures \(21 CFR 11\)](#)
 - [Financial Disclosure by Clinical Investigators \(21 CFR 54\)](#)
 - [Medical Device Reporting \(21 CFR 803\)](#)
 - [Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices \(21 CFR 807\)](#)
 - [In Vitro Diagnostic Products for Human Use \(21 CFR 809\)](#)
 - [Pre-market Approval of Medical Devices \(21 CFR 814\)](#)
 - [Medical Devices: Quality System Regulation \(21 CFR 820\)](#)
 - [Medical Device Classification Procedures \(21 CFR 860\)](#).
- E. For more information describing the FDA requirements for investigators and sponsors when research is initiated and conducted with investigational devices, see Attachments 3

and 4, respectively. Additional guidance describing the international standards for good clinical practices in human subjects research (“ICH/GCP”) is available at [ICH E6: Good Clinical Practice: Consolidated Guidance](#).

9. Humanitarian Use Devices

- A. An approved humanitarian device exemption (HDE), containing sufficient information for FDA to determine that the probable benefits outweigh the risks of a device’s use, is required for marketing a humanitarian use device. (Note: Results from scientifically valid clinical investigations demonstrating efficacy are not required for HDEs.) For a list of approved HDEs, see [Approved HDE Summaries of Safety and Possible Benefit](#).
- B. Humanitarian use devices are *marketed* products; therefore, their use does not constitute research when used according to the approved labeling. However, IRB approval is required before the HUD is used. FDA regulations require that initial IRB review and approval of the HUD occur at a convened meeting. Continuing review must be performed at least annually, but may be conducted by expedited review procedures.
- C. IRB review of HUDs should consider the criteria for approval (as applicable) described by regulations and OSU HRPP policy [[Review of Research by the Convened IRB](#)]. The following materials should be reviewed:
- HDE approval order
 - Description of the device
 - Product labeling
 - Patient information packet
 - Consent form
 - Summary of the proposed use of the device, including a description of any screening procedures, HUD procedure, and any follow-up visits, tests, or procedures for patients.

Patient information packets are available for most HUDs and generally contain a description of the potential risks and benefits of the HUD and any procedures associated with its use. The HDE approval order, product labeling, and patient information packet for an HUD can be obtained from the FDA website; see [Approved HDE Summaries of Safety and Possible Benefit](#).

- D. Informed consent should be obtained orally or in writing before HUD use. Minimally, the consent process should contain a discussion of the potential risks and benefits of the HUD, description of the procedures associated with its use, and a statement that the device is a “humanitarian use device” that has not undergone clinical testing for effectiveness. Use of the HUD should not be referred to as “research” or a “clinical investigation.” The IRBs will approve the consent process, its content, and any associated documents (i.e., consent form, information packet, etc.) that will be distributed

to recipients of the HUD. HIPAA research authorization is not also required, unless the HUD is used as part of a research study.

- E. FDA regulations require the institution and/or device manufacturer to report to FDA and the IRB deaths or serious injuries that may have been caused by an HUD or malfunctions that would “be likely to cause or contribute to a death or serious injury if the malfunction were to recur.”
- F. Investigational use of an HUD (i.e., for a broader or different indication than approved by FDA) requires an approved IDE in addition to IRB approval when the HUD is a significant risk device. For more information on HUDs, including investigational and emergency uses, see FDA guidance [HDE Regulation: Questions and Answers](#).

10. Custom Devices

FDA regulations do not require IRB review and approval for custom device use. However, to ensure adequate patient protections the requirements for the emergency use of devices, including prior notification, informed consent, and five-day reporting, should be followed when custom devices are used. For more information on these requirements, see OSU HRPP policy [[Emergency Use of Investigational Drugs, Biologics, or Devices](#)].

11. Applicable Regulations/Guidance

21 CFR 50; 21 CFR 56; 21 CFR 812; 21 CFR 814; FDA Guidance “Device Advice: Device Regulation and Guidance” (07/10/09), “Draft Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and FDA Staff - Humanitarian Device Exemption (HDE) Regulation: Questions and Answers” (08/05/08), and “E6: Good Clinical Practice: Consolidated Guidance” (04/96); FDA Information Sheets: “Frequently Asked Questions About Medical Devices,” “‘Off-label’ and Investigational Use of Marketed Drugs, Biologics, and Medical Devices,” and “Significant Risk and Nonsignificant Risk Medical Device Studies” (01/06)

Attachment 1.

Investigational Device Exemptions (21 CFR 812) Subpart A – General Provisions

Applicability

This part applies to all clinical investigations of devices to determine safety and effectiveness, except as provided in paragraph (c) of this section [812.2(c) *Exempted Investigations*].

Exempted Investigations

This part, with the exception of 812.119, does not apply to investigations of the following categories of devices:

1. A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
2. A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.
3. A diagnostic device, if the sponsor complies with applicable requirements in 809.10(c) and if the testing:
 - i. Is noninvasive,
 - ii. Does not require an invasive sampling procedure that presents significant risk,
 - iii. Does not by design or intention introduce energy into a subject, and
 - iv. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
4. A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.
5. A device intended solely for veterinary use.
6. A device shipped solely for research on or with laboratory animals and labeled in accordance with 812.5(c).
7. A custom device as defined in 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

Attachment 2.

Investigational Device Exemptions (21 CFR 812) Subpart A – General Provisions

Applicability

This part applies to all clinical investigations of devices to determine safety and effectiveness, except as provided in paragraph (c) of this section [812.2(c) *Exempted Investigations*].

Abbreviated Requirements

The following categories of investigations are considered to have approved applications for IDEs, unless FDA has notified a sponsor under 812.20(a) that approval of an application is required:

1. An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor:
 - i. Labels the device in accordance with 812.5;
 - ii. Obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;
 - iii. Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under 56.109(c);
 - iv. Complies with the requirements of 812.46 with respect to monitoring investigations;
 - v. Maintains the records required under 812.140(b) (4) and (5) and makes the reports required under 812.150(b) (1) through (3) and (5) through (10);
 - vi. Ensures that participating investigators maintain the records required by 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7); and
 - vii. Complies with the prohibitions in 812.7 against promotion and other practices.
2. An investigation of a device other than one subject to paragraph (e) of this section [812.2(e) *Investigations Subject to INDs*], if the investigation was begun on or before July 16, 1980, and to be completed, and is completed, on or before January 19, 1981.

Attachment 3.

Investigational Device Exemptions (21 CFR 812) Subpart E – Responsibilities of Investigators

812.100 General responsibilities of investigators

An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with part 50 of this chapter. Additional responsibilities of investigators are described in subpart G.

812.110 Specific responsibilities of investigators

- a. *Awaiting approval.* An investigator may determine whether potential subjects would be interested in participating in an investigation, but shall not request the written informed consent of any subject to participate, and shall not allow any subject to participate before obtaining IRB and FDA approval.
- b. *Compliance.* An investigator shall conduct an 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.
- c. *Supervising device use.* An investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized under this part to receive it.
- d. *Financial disclosure.* A clinical investigator shall disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required under part 54 of this chapter. The investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.
- e. *Disposing of device.* Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.

Subpart G – Records and Reports

812.140 Records

- a. *Investigator records.* A participating investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:
 1. All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.
 2. Records of receipt, use or disposition of a device that relate to:
 - i. The type and quantity of the device, the dates of its receipt, and the batch number or code mark.
 - ii. The names of all persons who received, used, or disposed of each device.
 - iii. Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.

3. Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include:
 - i. Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
 - ii. 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.
 - iii. A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.
4. The protocol, with documents showing the dates of and reasons for each deviation from the protocol.
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.
- d. Retention period. An investigator or sponsor shall maintain the records required by this subpart during the investigation and for a period of 2 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 pre-market approval application or a notice of completion of a product development protocol.
- e. Records custody. An investigator or sponsor may withdraw from the responsibility to maintain records for the period required in paragraph (d) of this section and transfer custody of the records to any other person who will accept responsibility for them under this part, including the requirements of 812.145. Notice of a transfer shall be given to FDA not later than 10 working days after transfer occurs.

812.145 Inspections

- a. *Entry and inspection.* A sponsor or an investigator who has authority to grant access shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept).
- b. *Records inspection.* A sponsor, IRB, or investigator, or any other person acting on behalf of such a person with respect to an investigation, shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation.
- c. *Records identifying subjects.* An investigator shall permit authorized FDA employees to inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.

812.150 Reports

- a. Investigator reports. An investigator shall prepare and submit the following complete, accurate, and timely reports:
 1. Unanticipated adverse device effects. An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
 2. Withdrawal of IRB approval. An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
 3. Progress. An investigator shall 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.
 4. Deviations from the investigational plan. An investigator shall notify the sponsor and the reviewing IRB (see 56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical wellbeing of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB in accordance with 812.35(a) also is required.
 5. Informed consent. If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.
 6. Final report. An investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.
 7. Other. An investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

Attachment 4.

Investigational Device Exemptions (21 CFR 812) Subpart C – Responsibilities of Sponsors

812.40 General responsibilities of sponsors

Sponsors are responsible for selecting qualified investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring that IRB review and approval are obtained, submitting an IDE application to FDA, and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation. Additional responsibilities of sponsors are described in subparts B and G.

812.42 FDA and IRB approval

A sponsor shall not begin an investigation or part of an investigation until an IRB and FDA have both approved the application or supplemental application relating to the investigation or part of an investigation.

812.43 Selecting investigators and monitors

- a. Selecting investigators. A sponsor shall select investigators qualified by training and experience to investigate the device.
- b. Control of device. A sponsor shall ship investigational devices only to qualified investigators participating in the investigation.
- c. Obtaining agreements. A sponsor shall obtain from each participating investigator a signed agreement that includes:
 1. The investigator's curriculum vitae.
 2. Where applicable, a statement of the investigator's relevant experience, including the dates, location, extent, and type of experience.
 3. If the investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to termination.
 4. A statement of the investigator's commitment to:
 - i. Conduct the investigation in accordance with the agreement, the investigational plan, this part and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA;
 - ii. Supervise all testing of the device involving human subjects; and
 - iii. Ensure that the requirements for obtaining informed consent are met.
 5. Sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement as required under part 54 of this chapter. The sponsor shall obtain a commitment from the clinical investigator to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study. This information shall not be submitted in an investigational device exemption application, but shall be submitted in any marketing application involving the device.
- d. Selecting monitors. A sponsor shall select monitors qualified by training and experience to monitor the investigational study in accordance with this part and other applicable FDA regulations.

812.45 Informing investigators

A sponsor shall supply all investigators participating in the investigation with copies of the investigational plan and the report of prior investigations of the device.

812.46 Monitoring investigations

- a. Securing compliance. A sponsor who discovers that an investigator is not complying with the signed agreement, the investigational plan, the requirements of this part or other applicable FDA regulations, or any conditions of approval imposed by the reviewing IRB or FDA shall promptly either secure compliance, or discontinue shipments of the device to the investigator and terminate the investigator's participation in the investigation. A sponsor shall also require such an investigator to dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.
- b. Unanticipated adverse device effects.
 1. A sponsor shall immediately conduct an evaluation of any unanticipated adverse device effect.
 2. A sponsor who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the sponsor makes this determination and not later than 15 working days after the sponsor first received notice of the effect.
- c. Resumption of terminated studies. If the device is a significant risk device, a sponsor may not resume a terminated investigation without IRB and FDA approval. If the device is not a significant risk device, a sponsor may not resume a terminated investigation without IRB approval and, if the investigation was terminated under paragraph (b)(2) of this section, FDA approval.

812.47 Emergency research under 50.24

- a. The sponsor shall monitor the progress of all investigations involving an exception from informed consent under 50.24 of this chapter. When the sponsor receives from the IRB information concerning the public disclosures under 50.24(a)(7)(ii) and (a)(7)(iii) of this chapter, the sponsor shall promptly submit to the IDE file and to Docket Number 95S-0158 in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, copies of the information that was disclosed, identified by the IDE number.
- b. The sponsor also shall monitor such investigations to determine when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception in 50.24(a) of this chapter or because of other relevant ethical concerns. The sponsor promptly shall provide this information in writing to FDA, investigators who are asked to participate in this or a substantially equivalent clinical investigation, and other IRBs that are asked to review this or a substantially equivalent investigation.

Subpart G – Records and Reports

812.140 Records

- b. *Sponsor records.* A sponsor shall maintain the following accurate, complete, and current records relating to an investigation:
 1. All correspondence with another sponsor, a monitor, an investigator, an IRB, or FDA, including required reports.
 2. Records of shipment and disposition. Records of shipment shall include the name and address of the consignee, type and quantity of device, date of shipment, and batch number or code

- mark. Records of disposition shall describe the batch number or code marks of any devices returned to the sponsor, repaired, or disposed of in other ways by the investigator or another person, and the reasons for and method of disposal.
3. Signed investigator agreements including the financial disclosure information required to be collected under 812.43(c)(5) in accordance with part 54 of this chapter.
 4. For each investigation subject to 812.2(b)(1) of a device other than a significant risk device, the records described in paragraph (b)(5) of this section and the following records, consolidated in one location and available for FDA inspection and copying:
 - i. The name and intended use of the device and the objectives of the investigation;
 - ii. A brief explanation of why the device is not a significant risk device;
 - iii. The name and address of each investigator;
 - iv. The name and address of each IRB that has reviewed the investigation;
 - v. A statement of the extent to which the good manufacturing practice regulation in part 820 will be followed in manufacturing the device; and
 - vi. Any other information required by FDA.
 5. Records concerning adverse device effects (whether anticipated or unanticipated) and complaints, and
 6. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation.
- c. **Retention period.** An investigator or sponsor shall maintain the records required by this subpart during the investigation and for a period of 2 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 pre-market approval application or a notice of completion of a product development protocol.
- d. **Records custody.** An investigator or sponsor may withdraw from the responsibility to maintain records for the period required in paragraph (d) of this section and transfer custody of the records to any other person who will accept responsibility for them under this part, including the requirements of 812.145. Notice of a transfer shall be given to FDA not later than 10 working days after transfer occurs.

812.145 Inspections

- a. **Entry and inspection.** A sponsor or an investigator who has authority to grant access shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept).
- b. **Records inspection.** A sponsor, IRB, or investigator, or any other person acting on behalf of such a person with respect to an investigation, shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation.

812.150 Reports

- b. **Sponsor reports.** A sponsor shall prepare and submit the following complete, accurate, and timely reports:
 1. **Unanticipated adverse device effects.** A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRBs and participating investigators within 10 working days

- after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.
2. *Withdrawal of IRB approval.* A sponsor shall notify FDA and all reviewing IRBs and participating investigators of any withdrawal of approval of an investigation or a part of an investigation by a reviewing IRB within 5 working days after receipt of the withdrawal of approval.
 3. *Withdrawal of FDA approval.* A sponsor shall notify all reviewing IRBs and participating investigators of any withdrawal of FDA approval of the investigation, and shall do so within 5 working days after receipt of notice of the withdrawal of approval.
 4. *Current investigator list.* A sponsor shall submit to FDA, at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. The sponsor shall submit the first such list 6 months after FDA approval.
 5. *Progress reports.* At regular intervals, and at least yearly, a sponsor shall submit progress reports to all reviewing IRBs. In the case of a significant risk device, a sponsor shall also submit progress reports to FDA. A sponsor of a treatment IDE shall submit semi-annual progress reports to all reviewing IRBs and FDA in accordance with 812.36(f) and annual reports in accordance with this section.
 6. *Recall and device disposition.* A sponsor shall notify FDA and all reviewing IRBs of any request that an investigator return, repair, or otherwise dispose of any units of a device. Such notice shall occur within 30 working days after the request is made and shall state why the request was made.
 7. *Final report.* In the case of a significant risk device, the sponsor shall notify FDA within 30 working days of the completion or termination of the investigation and shall submit a final report to FDA and all reviewing IRBs and participating investigators within 6 months after completion or termination. In the case of a device that is not a significant risk device, the sponsor shall submit a final report to all reviewing IRBs within 6 months after termination or completion.
 8. *Informed consent.* A sponsor shall submit to FDA a copy of any report by an investigator under paragraph (a)(5) of this section of use of a device without obtaining informed consent, within 5 working days of receipt of notice of such use.
 9. *Significant risk device determinations.* If an IRB determines that a device is a significant risk device, and the sponsor had proposed that the IRB consider the device not to be a significant risk device, the sponsor shall submit to FDA a report of the IRB's determination within 5 working days after the sponsor first learns of the IRB's determination.
 10. *Other.* A sponsor shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.