

## **Investigational Device Exemption Applications in FDA-Regulated Research**

### **Introduction and Purpose**

The conduct of a clinical investigation (i.e., clinical trial) under an FDA-Regulated Investigational Device Exemption (IDE) application includes a complex set of FDA regulations, requirements, and obligations. The FDA holds the sponsor of the IDE application responsible for ensuring that all of the regulations, requirements, and obligations are being met (21 CFR Part 812, Subpart C). Although sponsors of IDE applications are typically pharmaceutical and device companies, the FDA regulations governing IDE applications permit the sponsor to be an individual, governmental agency, or academic institution (21 CFR Part 812.3).

The purpose of this standard operating procedure is to:

- help determine when an IDE is required,
- provide guidance and resources to individuals conducting a clinical investigation, who may be sponsor-investigators, on obtaining an IDE for the device under study, and
- address the process for compassionate use (also referred to as expanded access) and emergency use of an investigational device.

### **IDE Definitions and Acronyms**

**510(k) Pre Marketing Notification:** A type of application to the FDA for high-risk Class III devices. In most cases, an IDE is required to clinically evaluate devices subject to PMA requirements.

**Classes of Devices:** The FDA has established three regulatory classes for devices, based on the level of control necessary to assure the device's safety and effectiveness. Device classification determines which type of premarketing submission or application is required to obtain FDA clearance to market a device.

- **Class I:** Very low-risk devices that are generally exempt from FDA regulations. All Class I medical devices are exempt from the requirement of premarket notification (510K) unless the device is intended for a use that is of substantial importance in preventing impairment to human health or presents a potentially unreasonable risk of illness or injury - examples: tongue depressors; stethoscopes; elastic bandages.
- **Class II:** Moderate-risk devices that are generally subject to 510(k) clearance. Clinical investigations are not required in most cases. However, if clinical data are necessary to demonstrate substantial equivalence to another device, the clinical study must comply with the IDE regulations. Class II devices are subject to labeling requirements, mandatory performance standards, and post-market

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surveillance, and are typically non-invasive. Examples include MRIs, software, powered wheelchairs, and surgical needles.

- **Class III:** Higher risk devices that require Premarket Approval (PMA). Clinical investigations are necessary to establish the safety and efficacy of the device. Insufficient information exists to assure safety and effectiveness solely through the general or special controls sufficient for Class I or Class II devices, or is of substantial importance in preventing impairment to human health, or presents a potential unreasonable risk of illness or injury. Class III devices are usually significant risk devices, but also include a few non-significant risk devices such as continuous glucose monitors and PSA tests. Examples of Class III devices include nonroller cardiovascular blood pumps, hemoperfusion systems for the treatment of hepatic coma and metabolic disturbances, and nonthermal shortwave diathermal devices.

**Device:** Any instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article which is recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement, and is intended:

- For use in the diagnosis of a disease or other conditions, or the cure, mitigation, treatment, or prevention of disease, in man or other animals.
- To affect the structure of any function of the body of man or other animals.
- It does not achieve its primary intentional purposes through chemical action and is not dependent upon being metabolized to achieve its primary intended purpose.
- Can include investigational software, whether it is stand-alone software meant for use on a general-purpose computer/other device, or it is a component of or accessory to another medical device (such as an MRI machine or CT scanner).

**Emergency Use:** The FDA Emergency Use exemption allows the use of an Investigational Device under strict criteria on a single subject in a life-threatening situation when no standard treatment is available. Emergency use is specifically emergency clinical care and is not considered research.

**Expanded Access:** The FDA has several specific mechanisms and regulations that allow use of an investigational device outside of a formal clinical trial. This is called expanded access. Expanded access, also called compassionate use, is the use of an investigational product outside of a clinical trial. Expanded access allows a patient to receive the product through expanded access when enrollment in a clinical trial is impossible. For example, a patient is not eligible for any ongoing clinical trials or there are no ongoing clinical trials. Prior IRB and FDA approval is required. One mechanism, an FDA approved Humanitarian Device Exemption (HDE) application, allows a device

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to be used clinically without having demonstrated efficacy. Although the FDA does not consider clinical use research, prior IRB approval is required. An HDE can also indicate FDA approval to use a HUD for research.

**HUD: Humanitarian Use Device:** A device that is intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.

**Investigational Device Exemption (IDE):** An investigational device is an item that is not FDA-approved for marketing in the United States, or an item that is being evaluated for a new and not-yet-approved use. An IDE is a request for authorization from the FDA to allow the use of an investigational device for human subjects.

**IDE Application:** An IDE application is the document submitted to the FDA for permission to conduct a clinical study using a significant risk device that is new or not approved for a given use. When the FDA receives an IDE application, it assigns an IDE number to the device's specific use. The FDA has 30 days to review the IDE submission and determine if the IDE application is approved. The IDE regulations are detailed in 21 CFR 812.

**Nonsignificant Risk Device:** An investigational device that does not meet the definition of a significant risk device. An IDE is not required for studies involving a nonsignificant risk device. For this reason, the FDA is usually not aware of the existence of these studies even after they receive IRB approval.

**PMA:** Premarket approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. The applicant must receive FDA approval of a PMA application prior to marketing the device.

**Significant Risk Device:** An investigational device that meets any of the following criteria. An IDE is required before the study can begin.

- Is intended as an implant and presents a potential for serious risk to a subject's health, safety, or welfare.
- Is purported or represented to be for use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject.
- Is for the 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;
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- Is classified by the FDA as a significant risk device.

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**Sponsor-Investigator:** A sponsor-investigator is an individual who both initiates and conducts the investigation and under whose immediate direction the investigational device is administered or dispensed. The requirements applicable to a sponsor-investigator includes both those applicable to an investigator and a sponsor.

<b>CFR:</b>	Code of Federal Regulations
<b>CRSO:</b>	Clinical Research Support Office
<b>FDA:</b>	United States Food and Drug Administration
<b>IRB:</b>	Institutional Review Board
<b>SOP:</b>	Standard Operating Procedure

### **IDE Support**

The IDE Specialist with the University of Utah Clinical Research Support Office (CRSO) assists sponsor-investigators with all aspects of the IDE process documented in this SOP. Sponsor-investigators within departments that do not provide IDE services should contact the CRSO IDE Specialist. Some departments may offer qualified IDE support. In such cases, sponsor-investigators are welcome to utilize their department resources. However, sponsor-investigators and department-specific IDE representatives are still welcome to collaborate with the CRSO IDE specialist if they have questions or require additional support. The CRSO IDE Specialist may be contacted by emailing [Jonna.Montgomery@hsc.utah.edu](mailto:Jonna.Montgomery@hsc.utah.edu).

### **IDE Guidance**

#### **1. IDE Requirements**

- 1.1 Investigations covered under the IDE regulation are subject to differing levels of regulatory control depending upon the level of risk.
- 1.2 The IDE regulation distinguishes between significant and nonsignificant risk device studies and the procedures for obtaining approval to begin the study differ accordingly.
- 1.3 All clinical investigations using devices must have an approved IDE or be exempt from the IDE regulations. Investigations that are exempt from 21 CFR 812 include:
  - 1.3.1 A legally marketed device, when used in accordance with its labeling.
  - 1.3.2 A diagnostic device, if it complies with the labeling requirements in §809.10(c), and if the testing:
    - Is non-invasive.
    - Does not require an invasive sampling procedure that presents

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significant risk.

- Does not by design or intention introduce energy into a subject.
- Is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure; consumer preference testing, testing of a modification, or testing of a combination of devices if the device(s) are legally marketed device(s) [that is, the devices have an approved PMA, cleared Premarket Notification 510(k), or are exempt from 510(k)] AND if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.
- A device intended solely for veterinary use.
- A device shipped solely for research with laboratory animals and contains the labeling, "CAUTION – Device for investigational use in laboratory animals or other tests that do not involve human subjects."

### **2. IDE Pre-Submission Process**

- 2.1 Sponsor-investigators are encouraged to contact the FDA to obtain further guidance prior to the submission of an IDE application. This is especially beneficial to new sponsors who have not previously had contact with the FDA and for sponsors proposing to study new technologies or new uses for existing technologies. Early interaction with the FDA will help increase the sponsor's understanding of the FDA requirements, regulations, and guidance documents. It will also allow the FDA's personnel to better understand the new technologies. Increased interaction between the FDA and sponsors may speed the regulatory process and minimize delays in developing useful devices intended for human use.
- 2.2 Pre-Submissions can be used to discuss potential or planned IDEs and can include discussions of clinical studies. The pre-submission can also be submitted to request the FDA's determination for whether a planned medical device clinical study is significant risk (SR), nonsignificant risk (NSR), or exempt from IDE regulations as defined by the IDE regulations (21 CFR 812).

### **3. Initial IDE Submission**

- 3.1 It is the responsibility of the sponsor-investigator to have the IDE application prepared and submitted to the FDA.
- 3.2 The content of each IDE differs depending on the investigational device and the study. A complete protocol, informed consent, and information about the investigational device are required for an IDE submission.
- 3.3 The FDA has 30 calendar days from receipt of the initial IDE package to review

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the submission. During the review, the FDA may request additional information and the sponsor-investigator needs to reply to all requests for information. During the 30-day review, the investigator may not begin the clinical study under submission.

3.4 After 30 calendar days from initial submission, the sponsor-investigator may begin the study, unless the FDA notifies the site that the study is on clinical hold or notifies the site earlier that the IDE may begin.

3.5 IRB Requirements:

3.5.1 The sponsor-investigator is responsible for ensuring that an IRB reviews and approves the study prior to beginning the study.

3.5.2 The University of Utah IRB may require that proof of IDE submission or waivers be submitted with the initial submission.

3.5.3 The University of Utah Pre-IDE Audit must be completed prior to IRB approval.

3.5.3.1 The IRB Pre-IDE Audit process is initiated automatically following IRB submission. During the pre-review period the sponsor-investigator will be contacted with details on how to initiate and complete the audit.

3.5.3.2 As part of the audit, the sponsor-investigator will be required to complete the Pre-IDE Checklist, which the IRB has made available here:

<https://irb.utah.edu/guidelines/fda-requirements/prop-initiated-studies.php>

3.5.4 For additional investigator responsibilities, please see the University of Utah UUSOP-4, located at:

<https://qualitycompliance.research.utah.edu/clinical-research-sops.php>.

### **4. Significant Risk Devices**

4.1 A significant risk device presents a potential for serious risk to the health, safety, or welfare of a subject. Significant risk devices may include implants, devices that support or sustain human life, and devices that are substantially important in diagnosing, curing, mitigating, or treating a disease or preventing impairment to human health. Examples include sutures, cardiac pacemakers, hydrocephalus shunts, and orthopedic implants.

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- 4.2 Studies of devices that pose a significant risk require both FDA and IRB approval prior to initiation of a clinical study. FDA approval is obtained by submitting an IDE application to the FDA.
- 4.3 In order to conduct a significant risk device study, a sponsor must submit a complete IDE application to the FDA for review and obtain FDA approval of the IDE; submit the investigational plan and report of prior investigations to the IRB at each institution where the investigation is to be conducted for review and approval; and select qualified investigators, provide them with all necessary information on the investigational plan and report of prior investigations, and obtain signed investigator agreements from them.
- 4.4 The FDA will notify the sponsor via email of the date it receives an IDE application. FDA may approve, approve with modification, or disapprove an IDE application. FDA may request additional information about an investigation. The sponsor may provide the requested information, or the sponsor may treat such a request as a disapproval of the application and request a hearing in accordance with 21 CFR 16.
- 4.5 The clinical investigation may begin after FDA and the IRB approves an IDE for the investigation. An investigation may begin 30 days after FDA receives the IDE application for the investigation of a device if IRB approval has been obtained unless FDA notifies the sponsor that the investigation may not begin.
- 4.6 Once an IDE application is approved, specific requirements must be met in order to conduct the investigation in compliance with the IDE regulations. The device must be labeled in accordance with the labeling provisions of the IDE regulations and must bear the statement, "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use."
- 4.7 Investigational devices can only be distributed to qualified investigators.
- 4.8 Each subject must be provided with and sign an informed consent form before being enrolled in the study.
- 4.9 All investigations must be properly monitored to protect the human subjects and assure compliance with approved protocols.
- 4.10 Commercialization, promotion, and misrepresentation of an investigational device, and prolongation of the study are prohibited.
  - 4.10.1 The IDE only allows the sponsor-investigator to use the device as described in the approved protocol under the current IDE. While commercialization and promotion of the device may be pursued following the study, FDA approval of a 510K or PMA application would

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be required prior to any marketing activity.

4.10.2 In order to prolong the study, an amendment would need to be submitted and approved under the current IDE.

4.11 The sponsor-investigator is required to maintain specified records and make reports to investigators, IRBs, and the FDA.

### **5. Non-Significant Risk Devices**

5.1 Nonsignificant risk devices are devices that do not pose a significant risk to human subjects. Examples include most daily-wear contact lenses and lens solutions, ultrasonic dental scalers, and Foley catheters.

5.2 A nonsignificant risk device study requires only IRB approval prior to initiation of a clinical study. Sponsor Investigators of studies involving nonsignificant risk devices are not required to submit an IDE application to the FDA for approval.

5.2.1 Submissions for nonsignificant device investigations are made directly to the IRB of each participating institution.

5.2.2 Sponsor-investigators should present to the reviewing IRB an explanation of why the device does not pose a significant risk. If the IRB disagrees and determines that the device poses a significant risk, the sponsor must report this finding to the FDA within five working days.

5.2.3 The FDA considers an investigation of a nonsignificant risk device to have an approved IDE when the IRB concurs with the nonsignificant risk determination and approves the study.

5.3 The sponsor-investigator must comply with the abbreviated IDE requirements.

5.3.1 The device must be labeled in accordance with the labeling provisions of the IDE regulation and must bear the statement, "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use."

5.3.2 The sponsor-investigator must obtain and maintain Investigational Review Board (IRB) approval throughout the investigation as a nonsignificant risk device study.

5.3.3 The sponsor-investigator must assure that investigators obtain and document informed consent from each subject according to 21 CFR 50, Protection of Human Subjects, unless documentation is waived by an IRB.

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- 5.3.4 All investigations must be monitored appropriately to protect the human subjects and assure compliance with approved protocols.
- 5.3.5 Sponsors-investigators are required to maintain specific records and make certain reports as required by the IDE regulation.
- 5.3.6 Sponsor-investigators must assure that participating investigators maintain records and make reports as required.
- 5.3.7 Commercialization, promotion, test marketing, misrepresentation of an investigational device, and prolongation of the study are prohibited.
  - 5.3.7.1 The IDE only allows the sponsor-investigator to use the device as described in the approved protocol under the current IDE. While commercialization and promotion of the device may be pursued following the study, FDA approval of a 510K application would be required prior to any marketing activity
  - 5.3.7.2 In order to prolong the study, an amendment would need to be submitted and approved under the current IDE.

### **6. IDE Reporting Requirements**

- 6.1 IDE Supplement
  - 6.1.1 Changes in the Investigational Plan
  - 6.1.2 Development Changes
  - 6.1.3 Changes in Clinical Plan
  - 6.1.4 New Facilities
- 6.2 Protocol Deviations
- 6.3 Unanticipated Adverse Event Reports – Within 10 days
- 6.4 Bi-Annual Report of Current Investigators
- 6.5 Annual Reports
  - 6.5.1 Due within 60 days of the anniversary date of the IDE filing.
  - 6.5.2 Must include the number of devices received, the number of devices used, a summary of anticipated and unanticipated adverse events during the reporting period, and the description of any deviations.
  - 6.5.3 Annual reports must be submitted even if the study has not yet opened.
- 6.6 Final Study Report

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6.6.1 A complete report of study results is submitted when all study activity is complete, and IDE will be closed.

### **7. IDE Submission Documentation**

7.1 The complete submission packet for all IDE submissions, FDA responses, and pertinent correspondence in support of the IDE should be retained for the duration of the study, and for a period of time following the completion of the study, in accordance with University of Utah Clinical Research SOP-06, "Study Records Management".

7.2 For studies utilizing the services provided by the University of Utah CRSO IDE Specialist, all FDA submission documents, responses, and correspondence for the IDE will be retained by the IDE Specialist and will not be filed in the regulatory/essential documents record for the study.

7.2.1 The study team is welcome to include a Note-to-File within the main regulatory/essential documents file indicating that the IDE and FDA documents are stored by the CRSO IDE Specialist in accordance with this SOP.

7.2.2 Requests to review IDE submission materials made by the study team and/or appropriate compliance entities will be accommodated by the CRSO IDE Specialist.

### **References**

- 21 CFR Part 812: Investigational Device Exemptions
- 21 CFR Part 812, Subpart C: Responsibilities of Sponsors
- 21 CFR Part 812.3: Definitions
- University of Utah Clinical Research SOP-06, Study Records Management: [https://qualitycompliance.research.utah.edu/resources/documents/uusop/uusop-06\\_study\\_records\\_management\\_17aug2020.pdf](https://qualitycompliance.research.utah.edu/resources/documents/uusop/uusop-06_study_records_management_17aug2020.pdf)

## Investigational Device Exemption Applications in FDA-Regulated Research

### Document Approval



3/12/2021

Andrew Weyrich, Ph.D.  
Vice President for Research, University of Utah

DATE

### Revision History

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Printed or photocopied versions are considered unofficial copies unless it is the original signed document.