Human Subject Protection Program
Investigator Guidance
October 5, 2022

CLINICAL INVESTIGATIONS OF DEVICES

Overview

- This guidance is intended to assist investigators in meeting the various Food and Drug Administration (FDA) requirements when using devices in clinical research (clinical investigations) and treatment.

- FDA IDE regulations 21 CFR 812 contain procedures and requirements for the clinical research involving devices. Clinical research involving devices **to determine safety and effectiveness of a device** are subject to these regulations, unless certain exemptions apply.

- For many studies involving devices, an investigator or sponsor must obtain an Investigational Device Exemption (IDE) from the FDA. All investigational device

studies involving human subjects must be submitted to the Institutional Review Board (IRB) for review and approval before the investigation can begin.

Investigational Drug Device Exemptions (IDEs)

A device is considered investigational if either condition applies:

- The device is not approved for marketing in the United States or
- The device is approved for marketing but is being clinically evaluated for a new indication.

An IDE is required for:

- **Studies involving unapproved devices that are considered to be significant risk:** An IDE from the FDA is required to perform clinical research using an unapproved device that poses a significant risk to subjects. Typically, these studies are conducted to collect safety and effectiveness data used to support Premarket Approval (PMA) applications submitted to the FDA. (See definitions below.)

- **Studies involving an approved device being tested for a new indication:** IDE regulations apply to significant risk studies testing an FDA-approved device for a new indication, and/or are being used or tested in a new way that significantly increases the risks associated with the device.

An IDE is not required for:

- Studies involving approved devices used within their approved labeling. Devices used within their approved labeling are exempt from IDE regulations.

- Studies involving devices that are considered to be non-significant risk (NSR): An IDE is not needed for research use of non-significant risk devices or devices that are substantially equivalent (510K) to currently marketed devices.

NSR Determinations:

- The IRB makes the NSR determination for device studies. The FDA authorizes IRBs to conduct the risk assessment of all proposed non-significant risk studies.

- Study approval is dependent on the Investigator supplying the IRB with sufficient information regarding the device and its intended use so that the IRB may conduct the risk assessment; as well as, an explanation of how the device meets the criteria for an NSR determination.

- If the IRB is unable to determine the device meets NSR criteria, the Investigator will need to contact the FDA for a formal determination.

FDA IDE-Exempt Studies

FDA regulations describe specific IDE-exempt studies.

Approved Device Used as Labeled

- The device is a transitional device.
- The device is FDA-Approved or cleared.
- The device has PMA approval, 510(k) clearance, or HDE approval.
- The device is Class I/II exempt from pre-market notification requirements.
- The device is an Automatic Class III (de novo) cleared device.

Diagnostic Devices

- The device is a diagnostic device.
- The sponsor will comply with applicable requirements in 21 CFR 809.10(c).
- The testing is noninvasive.
- The testing does not require an invasive sampling procedure that presents significant risk.
- The testing does not by design or intention introduce energy into a subject.
- The testing is not used as a diagnostic procedure without confirmation by another, medically established product or procedure.

Consumer Preference Testing

- The device is undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, and the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.

Custom Devices

- The device is a custom device as defined in 21 CFR 812.3(b) and is not being used to determine safety or effectiveness for commercial distribution.

Practice of Medicine

- A physician can use a legally marketed device for clinical purposes without IRB approval for any condition or disease within a "legitimate healthcare practitioner-patient relationship". However, the results of an off-label use of a medical device cannot be presented as research.

Humanitarian Device Exemptions (HDEs)

- An HDE is a type of Premarket Application described under the Safe Medical Devices Act (SMDA) of 1990 and allows the FDA to grant an exemption from the effectiveness requirements of the Premarket Approval (PMA) regulations.

- Devices approved under an HDE are referred to as a Humanitarian Use Device (HUD). The provisions for obtaining an HDE are:

  - ☐ The device is designed to treat or diagnose a disease or condition that affects fewer than 4,000 individuals per year in the U.S.;

  - ☐ The device is not available otherwise, and there is no comparable device available to treat or diagnose the disease or condition; and

  - ☐ The device will not expose patients to unreasonable or significant risk, and the benefits to health from the use outweigh the risks.

- Treatment under an HDE is not considered research, but the FDA requires IRB review prior to use. The IRB requires a standard iStar application and use of a consent form, information sheet or device brochure similar to a research consent.

- HUDs that are used for research (clinical investigation) are subject to the requirements of part 812, which may require the submission of an IDE to the FDA.

Differences Between a "Sponsor" and a "Sponsor-Investigator" IDE

The FDA makes the following distinction between a "sponsor" and a "sponsor-investigator" and a "commercial IDE" and an "Investigator-Initiated IDE."

- **"Sponsor"** means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or company, governmental agency, academic institution, private organization, or other organization. The sponsor does

not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor investigator, and the employees are investigators.

- **"Sponsor-Investigator"** means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational device is used. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

- A **"Commercial IDE"** is submitted by a sponsor seeking FDA clearance to market a medical device.

- An **"Investigator-Initiated IDE"** is submitted by a physician who both initiates and conducts the clinical investigation.

Submitting an IDE to the FDA

- **Pre-IDE Process:** Investigators considering submitting an IDE application to the FDA should communicate with the reviewing division of the Office of Device Evaluation (ODE) prior to the submission of an IDE application. See the FDA IDE Approval Process website for details.

- **IDE Submission:** The IDE submission to the FDA and the IRB application should be initiated at the same time. The FDA has 30 days to review the IDE application. Likewise, the IRB typically reviews an application within a 30-day window, but it may take longer to secure approval. Subjects may not be recruited or enrolled before FDA and IRB approval.

Expanded Access and Emergency Use of Unapproved Devices for Treatment

- The FDA allows certain individuals not enrolled in clinical trials to obtain expanded access to investigational devices through expanded access programs. Refer to the Investigator guidance document, "Expanded Access and Emergency Use of a Test Article" for more details.

IRB Review Requirements

If the study involves testing the safety and/or effectiveness of a device, the investigator should check “Approved/Investigational Devices” in the iStar application. By doing so, the investigator will be prompted to answer the appropriate questions and provide the information needed for IRB review.

- **Approved Device Used as Labeled:** Evidence of FDA approval and a description of the FDA approved indications must be provided by the Sponsor/Investigator (e.g., PMA letter, 510(k) letter, HDE letter, Class I/II exemption category, de novo designation letter).

- **NSR Determinations:** The Investigator must provide an explanation that the device is NSR by completing the NSR determination form that is available on the CHLA HSPP website. This form needs to be included in the IRB application.

- **IDE Verification:** The CHLA IRB may review the research before the IDE application is submitted to or approved by to the FDA. The FDA does not require local IRB approval before issuing an IDE number. When a clinical investigation requires an IDE number, the IRB will not issue final approval until the IDE number is reported to and verified by the IRB. Verification can be accomplished by providing the following:

  ☐ Sponsor protocol imprinted with the IDE/HDE number, or

  ☐ Written communication from the sponsor documenting the IDE/HDE number, or

  ☐ Written communication from the FDA documenting the IDE/HDE number. **NOTE:** This option is required if the CHLA investigator holds the IDE/HDE.

- **Investigator’s Brochure**: For any study involving an investigational device that poses a significant risk to subjects, a copy of the device brochure should accompany the IRB application. For studies involving non-significant risk devices, manuals, diagrams and/or in situ photographs of the device are helpful.

- **Protocol:** If there is a sponsor or multicenter protocol, a copy of that protocol must accompany the IRB application.

- **Information about the device**: Including the trade (brand) name of device, common (generic) name of device, manufacturer of the device (if CHLA research lab, identify

the lab), source of the device, directions for use, device brochure (if appropriate and/or available).

- **Charging for the costs of the device:** The FDA IDE regulations allow sponsors to charge for an investigational device, however, the charge cannot not exceed an amount necessary to recover the costs of manufacture, research, development, and handling of the investigational device [21 CFR 812.7(b)]. Documentation of FDA approval to charge for the costs of the device must be submitted with the application.

Control of Investigational Devices

- Investigators conducting studies in which an investigational device will be used must ensure adequate control of the device in accordance with CHLA Policy Number FIN 010.0.

FDA References and Regulations

FDA References:

- Device Advice: Comprehensive Regulatory Assistance
- Significant Risk and Non-significant Risk Medical Device Studies
- Expanded Access to Unapproved Medical Devices
- Humanitarian Device Exemption Program
- Premarket Notification 510(k) Clearances
- FDA Devices Exempt from Premarket Notification 510(k)
- Premarket Approval Application (PMA) Approvals
- FDA Device Classification Database (searchable)

FDA Regulations:

- Investigational Device Exemptions: 21 CFR 812
- Premarket Approval of Medical Devices (includes HUDs): 21 CFR 814
- Medical Device Classification Procedures: 21 CFR 860