Investigational Devices

Investigational test articles are only allowed to be used in approved research protocols under the direction of approved researchers. Clinical investigations undertaken to develop safety and effectiveness data for medical devices must be conducted according to the requirements of Investigational Device Exemptions (IDE) regulations (21 C.F.R. part 812). Certain clinical investigations of devices (example, certain studies of lawfully marketed devices) may be exempt from the IDE regulations {21 C.F.R. 812.2(c)}. Unless exempt from the IDE regulations, an investigational device must be categorized as Significant Risk (SR) or Non-Significant Risk (NSR).The determination is initially made by the sponsor. The proposed study is then submitted to the FDA (for SR studies) or to an IRB (for NSR studies).

Definitions:

Investigational device - a device, including a transitional device, that is the object of an investigation.

Investigational device exemption (IDE) - IDE refers to the regulations under 21 CFR 812. An approved IDE means that the IRB (and FDA for significant risk devices) has approved the sponsor's study application and all the requirements under 21 CFR 812 are met.

Significant risk device - Significant risk device is an investigational device that: (1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; (2) is for use in supporting or sustaining human life and represents a potential for serious risk to the health, safety, or welfare of a subject; (3) is 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 (4) otherwise presents a potential for serious risk to a subject.

IDE Exemptions

Studies exempt from the IDE regulations include:

- a legally-marketed device when used in accordance with its labeling
- a diagnostic device if it complies with the labeling requirements in §809.10(c) and the testing is noninvasive
- does not require an invasive sampling procedure that presents 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

Significant risk (SR) and non-significant risk (NSR) devices

Significant risk devices:

Research with devices falls into three (3) categories:
- Investigations of significant risk devices to determine safety and effectiveness of the device
- Investigations of non-significant risk devices to determine the safety and effectiveness of the device
- Investigations exempted under the regulations Studies that include medical device use in an incidental way, where the device or the use of the device is not the focus of the research, are generally not considered to be FDA-regulated research or subject to 21 CFR 812, and in some instances are eligible for IRB review according to the expedited procedure (45 CFR 46.110 and 21 CFR 56.110).

In order to conduct a research study with a significant risk device, a sponsor must:
- Submit a complete IDE application (§812.20) to FDA for review
- Obtain FDA approval of the IDE
- Submit the research plan to the IRB where the investigation is to be conducted for review and approval
- Select qualified investigators and obtain signed investigator agreements

The following requirements must be followed 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 (812.5)
- Investigational devices may only be distributed to qualified investigators
- Each subject must be provided with and sign an informed consent form prior to enrollment
- All investigations must be properly monitored to protect subjects and assure compliance with the approved protocol
- Commercialization, promotion, and misrepresentation of an investigational device and prolongation of the study are prohibited
- Sponsors and investigators must maintain specified records and supply reports to investigators, IRB, and FDA

<u>Nonsignificant Risk Devices</u>

A nonsignificant risk device study only requires IB approval prior to initiation of the clinical study. Sponsors of NSR device studies are not required to submit an IND application to FDA for approval. The sponsor is required to conduct the study in accordance with an abbreviated set of requirements [21 C.F.R. 812.2(b)]. An approval letter from the sponsor verifying the determination of NSR status may be required for the IRB review.

Sponsors should provide the reviewing IRB an explanation as to why the device does not pose a significant risk. If the IRB disagrees with the sponsor's risk assessment, the sponsor must report this finding to the FDA within five working days [§812.150 (b) (9)]. FDA considers the NSR

device to have an approved IDE when the IRB concurs with the NSR determination from the sponsor and approves the study.

The sponsor must also comply with abbreviated IDE requirements under §812.2 (b):

- Label the device in accordance with the labeling provisions of the IDE regulations
- Obtain and maintain IRB approval
- Ensure investigators obtain and document informed consent from subjects
- All investigations must be properly monitored to protect subjects and assure compliance with the approved protocol
- Sponsors must maintain specified records and supply reports as required by the IDE regulations
- Ensure that investigators maintain records and make reports as required
- Commercialization, promotion, and misrepresentation of an investigational device and prolongation of the study are prohibited

Submitting an IDE Application to FDA

The sponsor is responsible for submitting the IDE application to the FDA and obtaining IRB approval before a study can begin. The Human Protections Administrator (HPA) will verify the IDE. Under some circumstances, the investigator may wish to submit an IDE and would act as the sponsor of the study.

Instructions and guidance for the IDE application can be found at https://www.fda.gov/medical-devices/device-advice-investigational-device-exemption-ide/ide-application

The review of applications by the FDA and the IRB are independent and may be submitted simultaneously. IRB approval and an approved IDE must be obtained before beginning the study.

Questions about whether a product is subject to IDE regulations: call FDA 301-796-5640

IRB Review of NSR/SR Device Studies

The IRB's SR/NSR determination has significant consequences for the study sponsor, FDA, and prospective research subjects. SR device studies must be conducted in accordance with the full IDE requirement and may not commence until 30 days following the sponsor's submission of an IDE application to the FDA. The study may not proceed until the FDA has approved the IDE application and the IRB has approved the study. If the sponsor and the IRB disagree on the NSR determination, the FDA is the final arbiter. The IRB should document the NSR or SR determination in the IRB meeting minutes.

The IRB will follow the procedures outlined for full committee review and continuing review. Some NSR studies may qualify as minimal risk studies and be reviewed through an expedited

review process. All SR studies present more than minimal risk and full board IRB review is necessary.

To assist in its determination of the risk status of a device, the IRB requests that the sponsor submit reports of prior investigations conducted with the device, the proposed investigational plan, a description of the subject selection criteria, and monitoring procedures [21CFR812.150(b)(10)]. In addition, the IRB uses the following FDA Information Sheets: "Significant Risk and Non-significant Risk Medical Device Studies" and "Sponsor-Investigator-IRB Interrelationship" documents to assist in SR/NSR determinations.

The IRB should consider the basis for the risk determination, the nature of the harm that may result from use of the device, and if subjects will need to undergo additional procedures as part of the investigational study. If the IRB agrees with the sponsor's initial NSR assessment and approves the study, the study may begin without the submission of an IDE application to the FDA. If the IRB disagrees, the sponsor must notify the FDA that an SR determination has been made. The study can be conducted as a SR investigation following FDA approval of an IDE application.

If the IRB considers the study to be SR, the IRB will notify the investigator and, when appropriate, the sponsor, and request that the sponsor obtain an IDE from the FDA before proceeding with the study. If SR, the study may not begin until approval from FDA with an IDE application. The IRB may ask for documentation of the SR device IDE application.

The FDA has the ultimate decision in determining the risk of a device. If the FDA does not agree with the IRB's decision that a device study presents a NSR, an IDE application must be submitted to the FDA. If a sponsor files an IDE with FDA because it is presumed to be an SR study, but the FDA classifies the device study as NSR, the FDA will return the IDE application to the sponsor and the study would be presented to the IRB as a NSR investigation. It is unlikely that a device included in the SR category could be deemed NSR due to the inherit risks associated with most such devices. The list of devices provided by the FDA is not definitive and is subject to additions and deletions. Investigators are encouraged to check with the FDA for the latest list of medical devices. The HPA will verify the IDE for any studies submitted.

Storage and Use of Investigational Devices

Where allowed or required, the researcher may assign some or all duties for investigational device accountability to an appropriate pharmacist or another appropriate individual who is under the supervision of the researcher. Records should include:

- The products' delivery to the site
- The inventory at the site
- The use by each participant
- Return to the sponsor (or alternative disposition) of unused products

The records should include dates, quantities, batch/serial/lot numbers, expiration dates (if applicable), and any unique code numbers assigned to the investigational devices and participants. The records should reconcile all investigational devices received from the sponsor.

If device is not a physical instrument (such as an app or software), the researcher should include a plan in the protocol that explains that the device is used only for the specific research study and that access will be limited to members of the study team.