protocol, and (c) the FDA-approved informed consent document. An IRB Chair will review the document and decide whether a local IRB review is needed, then the IRB Chair's decision will be communicated to the investigator in writing.

## 8.6 INVESTIGATIONAL USE OF MEDICAL DEVICES

All clinical investigation of medical devices must comply with FDA regulations for investigational device exemptions (21 CFR 812).

*Medical Device:* an instrument, apparatus, implement, contrivance, implant, in vitro reagent, or other similar or related article, including component, part, or accessory, which is: (a) recognized in the official national Formulary, or the United States Pharmacopoeia, or any supplement to them; (b) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in humans; or (c) intended to affect the structure or any function of the human body; and does not achieve any of its principal intended purposes through chemical action within or on the human body and is not dependent upon being metabolized for the achievement of its principal intended purposes.

*Investigational Device:* a device that is the object of an investigation. Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices.

*Investigation:* a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.

*Medical Device Labeling:* any label or written material on the device or material that accompanies the device. This can include instructions for use, advertising and promotional material. This information must be provided to the FDA during the Premarket Approval (PMA) process. Labeling must provide adequate directions for use, unless it is exempt; it cannot be false or misleading.

*In Vitro Diagnostics (IVDs):* Reagents, instruments and systems intended for use in the diagnosis of disease or other conditions, including a determination of state of health, in order to cure, mitigate, treat or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. IVDs are medical devices as defined in section 210(h) of the Federal Food, Drug, and Cosmetic Act, and may also be biological products subject to section 351 of the Public Health Service Act. Like other medical devices, IVDs are subject to premarket and postmarket controls. IVDs are also subject to the Clinical Laboratory Improvement Amendments (CLIA '88) of 1988. Under FDA's regulations governing the conduct of IVD device studies, the definition of "subject" includes individuals on whose specimens an investigational device is used (21 CFR 812.3(p)). As a result, an IVD study using human specimens involves human subjects. IVDs require an IDE if the proposed IVD study does not meet an exemption in 21 CFR 812.2. The requirements for an IDE depend on the level of risk that the study.

### A. Investigational Device Exemption (IDE)

An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data. Clinical studies are most often conducted to support a PMA. Only a small percentage of 510(k)s require clinical data to support the application. Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices. All clinical evaluations of

investigational devices, unless exempt, must have an approved IDE before the study is initiated.

Clinical evaluation of devices that have not been cleared for marketing requires:

1. an investigational plan;
2. informed consent from all patients;
3. labeling stating that the device is for investigational use only;
4. monitoring of the study; and
5. required records and reports.

An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with other requirements of the Food, Drug, and Cosmetic Act (FD&C Act) that would apply to devices in commercial distribution.

**B. Exemption from IDE Requirements**

The device fulfills one of the IDE exemption categories (21 CFR 812.2) (and thus, does not require an IDE application to be filed with the FDA) when it is:

i. Exemption 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.

ii. Exemption 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 in determining substantial equivalence

iii. Exemption 3

- A diagnostic device (e.g., an *in vitro* diagnostic device) if 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, and
    - Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

iv. Exemption 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.

v. Exemption 7

- A custom device, as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution

Clinical investigations that are exempt from IDE regulations still require IRB review and approval.

### C. Determination of Significant Risk and Non-Significant Risk

Sponsors are responsible for making the initial risk determination and presenting it to the IRB with sufficient evidence for the determination. Unless the FDA has already made a risk determination for the study, the IRB must review the sponsor's significant risk (SR) or non-significant risk (NSR) determination for every investigational device study and review and modify the determination if the IRB disagrees with the sponsor's assessment. If the FDA has already made the SR or NSR determination for the study, the agency's determination is final, and the IRB need not duplicate the assessment. If the IRB assigns a device NSR status but the FDA does not agree, the FDA may overrule the IRB's decision and require that the sponsor submit an IDE application. If a sponsor has filed an IDE but the FDA then classifies the device study as NSR, the FDA will return the IDE application to the sponsor and the IRB should be informed of the FDA's determination. If necessary, the IRB may consult with the FDA before making a determination of SR/NSR.

For studies that are exempt from the IDE regulations, the IRB does not need to make an SR or NSR determination. However, the IRB must still review the study in accordance with the IRB regulations before the investigation may begin.

Under 21 CFR 812.3(m), a SR device means an investigational device that:

i. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

ii. Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;

iii. 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

iv. Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

If the device presents a significant risk to subjects, the sponsor must apply for an IDE from the FDA. If the device does not pose significant risks to subjects, justification for the NSR determination must be indicated on the IRB application in Cayuse IRB. NSR is an investigational device that does not meet the definition for a SR device.

Sponsors must provide the IRB with sufficient technical information about the device, reports of prior investigations conducted with the device, documentation of other IRBs' determinations about the study, and an indication of whether the FDA has determined the risk category on the device to facilitate the IRBs decision about its risk status.

The IRB makes the risk determination by reviewing relevant information at a convened meeting, including the following:

- The description of the device;

- Prior investigations conducted with the device;
- The proposed use and investigational plan;
- The subject selection criteria;
- The nature of any harm that may result from the use of the device;
- The potential harm of any additional procedures needed as part of the investigational study.

The IRB meeting minutes will document the rationale for SR/NSR assignment in addition to subsequent approval or disapproval decisions for the clinical investigation. If the IRB determines the study is an NSR device study, the study may begin without submission of an IDE application to the FDA. If the IRB disagrees with the sponsor's NSR assessment and decides the study is an SR device study, the sponsor must obtain an IDE from the FDA. The IRB considers investigation of any SR device to present greater than minimal risk; thus, full IRB review is required for all studies involving SR devices.

**D. 510(k) Device**

A 510(k) device refers to a new device that the FDA determines to be substantially equivalent to a device that was marketed prior to passage of the Medical Device Amendments of 1976 [510(k) refers to the section of the Food, Drug and Cosmetic Act that describes pre-market notification]. Devices that qualify as 510(k) devices may be marketed immediately without additional investigation of safety and efficacy. Research activities involving a 510(k) device do not require an FDA Investigational Device Exemption (IDE) prior to approval by the IRB; however, the IRB should be provided with documentation of the FDA's determination that the device qualifies as a 510(k) device.

**E. Reporting Requirements for Investigational Device Studies**

i. Investigators must submit to the sponsor and to the IRB a report of any unanticipated adverse device effect or problem that places subjects or others at a greater risk of harm 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.

ii. Investigators must report to the sponsor, within 5-working days, a withdrawal of approval by the IRB of the investigator's part of an investigation.

iii. Investigators must notify the sponsor and the IRB of any deviation from the investigational plan to protect the life or physical well-being of a research subject in an emergency. Such notice must be given as soon as possible, but in no event later than 72 hours to the IRB and 5-working days to the sponsor 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 participants, FDA and IRB in accordance with 21 CFR 812.35(a) also is required.

iv. If an investigator uses a device without obtaining informed consent, the investigator must report such use to the sponsor and the IRB within 5-working days after the use occurs.

v. Investigator must, 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 IRB.

## F. Continued Access

FDA may allow continued enrollment of subjects after the controlled clinical trial under an IDE has been completed in order to allow access to the investigational device while the marketing application is being prepared by the sponsor or reviewed by FDA.

The sponsor of a clinical investigation is permitted to continue to enroll subjects if there is:

- A public health need for the device; or
- Preliminary evidence that the device is likely to be effective and no significant safety concerns have been identified for the proposed indication.

Extended investigations permit patients and/or physicians continued access to the devices while also allowing the collection of additional safety and effectiveness data to support the marketing application or to address new questions regarding the investigational device. A sponsor's request for Continued Access should be submitted as an IDE supplement.

If the IDE application for the Continued Access of the device is approved by the FDA, the physician should submit the following in an Initial Application in Cayuse IRB:

- The current, written original clinical trial protocol for reference.
- A written summary describing the device use; including the rationale for the use, an explanation of why the use of the investigational device is preferable to the use of available marketed treatments; and a description of the clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the device and minimize its risks.
- Information that is relevant to the safety and effectiveness of the device for the intended continued use. A description of the data to be collected for support of the marketing application.
- A copy of the written consent form that will be used to obtained informed consent. The consent form must contain all the elements of consent per FDA regulations, and must explain the purpose of the use of this device, and the description of the data that will be collected to report safety and effectiveness data to the FDA and sponsor or collected in support of the device approval.
- The approval from the FDA of the IDE supplement for the Continued Access.
- A statement from the sponsor of the IDE supplement that they will provide the device; including a description of what costs the patients will incur, if any, from the use of the device.

Once the review is submitted to the IRB, the Continued Access documents will be reviewed at a convened IRB meeting, following standard IRB procedures. All Continued Access IDEs do not meet the criteria for expedited review and it must go to the full IRB for review. Since it involves the use of an investigational device, it does not qualify as minimal risk.