Florida State University Human Subjects Committee

Standard Operational Procedure (SOP) 7-IRB-46

Title:	Procedures for Investigational Devices
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1 INTRODUCTION

The purpose of this Standard Operational Procedure (SOP) is to determine when an Investigational Device Exemption (IDE) is required and establish definitions and procedures for investigators and/or investigator-sponsors holding an IDE for the test article being studied. This SOP applies to all human subjects research falling under the purview of the Florida State University Institutional Review Board (IRB).

An IDE allows an investigational/unapproved device to be used in a study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification (510(k)) submission to the Food and Drug Administration (FDA). Note that this can also include an evaluation of modifications to or new intended uses of legally marketed devices. All investigational devices, unless determined to be exempt, must have an approved IDE prior to initiation of a study. Not all investigational devices will need an IDE determination from the FDA if the device satisfies FDA criteria for non-significant risk devices (NSR) or is determined to be exempt; however all device studies must comply with certain guidelines as outlined in this SOP. The intended use of the device is the driving force for the determination of the regulatory pathway application to FDA.

1.1 The role of the IRB

The IRB has neither the responsibility nor authority to determine whether an IDE is necessary. The FDA has specified that the IRB's role is to ask the researcher whether an IND or IDE is required and the basis for that determination. The IRB's determination about the risk of a device interacts with the need for an IDE. If the IRB believes the study requires an IDE but the investigator (or investigator-sponsor) does not, the IRB has the authority to require contact with the FDA to determine whether an IDE is required. The IRB's determination of NSR/SR is a separate and independent process from risk/benefit determination for the study itself. If the FDA has already made a risk determination for the study, the agency's determination is final and should be submitted to the IRB with the study

application. However, if FDA determines a device to be NSR, the IRB can override that determination if it feels the device is SR.

The device Principal Investigator is responsible for the control of devices under investigation and will therefore be required to provide a plan – to be evaluated by the IRB - that includes storage, security, and dispensing of the device, and will be responsible for accounting, return, disposition, and records of accountability per the study protocol. If the IRB determines that it does not have the necessary expertise to evaluate the plan, outside consultation may be used as per SOP **7-IRB-17**.

Note that this SOP does not address emergency or compassionate use.

1.1 Definitions

1.1.1 Device

A device is an 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. This definition can include component parts or accessories, assays, and certain electronic products. A device can include investigational software. A device's intent for use must be for the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, or is intended to affect the structure or function of the body of man or other animals. A device does not achieve its primary intentional purposes through chemical action or by being metabolized by the body.

1.1.2 Sponsor

The person, company, organization, or other entity that initiates and takes responsibility for a clinical investigation using an FDA-regulated item. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. The item is administered, dispensed, or used under the immediate direction of another individual.

The sponsor is almost always the holder of an IND or IDE when the research involves an item that the FDA considers investigational.

1.1.3 Sponsor-investigator

An individual who both initiates and actually conducts, alone or with others, a clinical investigation, under whose immediate direction the test item is administered, dispensed or used. This term does not include any entity other than an individual. A sponsor-investigator has the responsibilities of both a sponsor and an investigator.

1.1.4 Premarket Approval (PMA)

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 regulations.

1.1.5 Pre-marketing Notification (510(k))

A type of application to the FDA, used for Class I, Class II, and some Class III devices which the sponsor believes have "substantial equivalence" to the safety and effectiveness of an already-approved device.

1.2 Categories of devices

FDA places all investigational devices it approves for clinical trials into one of two categories. The category will be provided in the IDE approval letter from the FDA, if this is the route taken. The purpose of categorization is to assist with Medicare and Medicaid coverage decisions. Category A items are not covered under Medicare and Medicaid.

1.2.1.1 Category A – Experimental

This IDE category is for an innovative device for which "absolute risk" has not been established. Initial questions of safety and effectiveness have not been resolved and thus FDA is unsure whether the device type can be safe and effective.

1.2.1.2 Category B – Investigational; Non-experimental

The clinical investigation involves a device type believed to be in Classes I or II, or device type believed to be in Class III where the incremental risk is the primary risk in question (i.e., underlying questions of safety and effectiveness of that device type have been resolved). This category includes device types that can be safe and effective because other manufacturers have obtained FDA approval for that device type. Non-significant risk studies may also be included in this category.

1.3 Classes of medical devices

As part of the Federal Food, Drug and Cosmetic Act, FDA has established three regulatory classes for devices, based on the level of control necessary to assure the safety and effectiveness of the device. These classifications are risk-based and occurs via the medical device product classification designated under 21 CFR Parts 862-892. Device classification determines which type of premarketing submission or application is required in order to obtain FDA clearance to market a device. The Product Code Classification Database may be consulted to identify the generic category of a device.

1.3.1 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.

1.3.2 Class II

Moderate risk devices that are generally subject to "510K 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. Subject to labeling requirements, mandatory performance standards, and post-market surveillance. Typically non-invasive. Examples: MRIs; software, powered wheelchairs, surgical needles.

1.3.3 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.

2 PROCEDURES

The use of investigational devices must comply with all federal, state or local regulations. FDA regulations apply to any test article in a clinical investigation involving human subjects as defined by the FDA. The IRB must apply FDA regulations at 21 CFR 50 and 21 CFR 56, as well as 45 CFR 46, if applicable.

The investigator is responsible for the control of devices under investigation and is required to submit a plan for IRB review that includes storage, security and dispensing of the device as well as accounting, return, disposition and records of accountability as stated in the research protocol. If the IRB determines that it does not have the necessary expertise to evaluate the plan, outside expertise as per FSU SOP **7-IRB-17** may be utilized.

Unless the FDA has already made a risk determination for the study, the IRB will review devices to determine if the device represents significant risk (SR) or non-significant risk (NSR) and will document this review. The sponsor or investigator-sponsor should make an initial determination at the time of submission to the IRB. If the IRB designates the device as SR, the sponsor or investigator-sponsor will be required to submit to the FDA for an IDE. The study will not be approved by the IRB until the IDE is obtained. The investigator will be informed of the IRB's determination in writing and if applicable, the investigator must notify the sponsor. NSR studies do not need to be submitted to the FDA, but must be conducted in accordance with abbreviated requirements of IDE regulations, as noted below.

2.1 Human Subjects Office Pre-Review

The Human Subjects Office staff will conduct a pre-review of the application materials provided by the researcher to determine the level of IRB review and verify application materials required for review are present in the application. The Human Subjects Office staff will also verify appropriate trainings for investigators involved with the research project (Human Subjects Training, GCP training).

2.2 IRB Process for Risk Determination

IRB review will include considerations of risks and benefits of the device compared to the risks and benefits of alternative devices.

2.2.1 Determination as to whether a device can be exempt from IDE requirements

The first step is to determine whether the device is exempt from IDE requirements as per CFR 812.2(c). It is the sponsor's (or investigator-sponsor's) responsibility to provide adequate justification to the IRB to support an exemption being claimed. In the IRB application, the explanation should include a reference to the applicable exemption category.

There are seven potential categories for exemption as per CFR 812.2(c).

For devices, an IDE is not necessary if:

1. The research involves 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. The research involves 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 21 CFR 807 in determining substantial equivalence;
3. The research involves a diagnostic device, if the sponsor complies with applicable requirements in 21 CFR 809.10(c) and 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;
4. The research involves 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. The research involves a device intended solely for veterinary use;
6. The research involves a device shipped solely for research on/or with laboratory animals and labeled in accordance with 21 CFR 812.5(c);
7. The research involves 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.

If a device is not exempt from the IDE requirements, an appropriate risk category must be determined. This will be based on the proposed use of the device in the context of the investigation (not just on the device alone).

2.2.2 Significant Risk (SR) and Nonsignificant Risk (NSR) or Humanitarian Use Device (HUD) determination

The IRB will review a device to determine the appropriate risk category. The IRB will document in the meeting minutes and in written correspondence to the investigator (or investigator-sponsor) determination that a device is significant or non-significant risk. The IRB minutes will outline the reason for the determination.

Significant Risk (SR) [Device]: 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; or
2. Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; or

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 the health, safety, or welfare of a subject.

Non-Significant Risk (NSR) [Device]: an investigational device other than a significant risk device.

Humanitarian Use Device (HUD): a device intended to benefit patients by treating or diagnosing a disease that affects fewer than 8,000 individuals in the United States per year. Although it is not anticipated that this category will be utilized in this institution, the information is included to address the potential it does occur.

2.2.3 Actions following IRB determination of risk for a device

Significant Risk (SR) [Device]: If the IRB identifies the device as SR, the investigator will notify the sponsor (or investigator-sponsor) of the SR determination**.** The FDA must be consulted, and an IDE must be obtained from the FDA and submitted to the IRB for full approval to proceed with the investigation. These studies are subject to full regulatory requirements as per FDA.

Non-Significant Risk (NSR) [Device]: If the IRB identifies the device as NSR, the determination will be communicated to the sponsor (or investigator-sponsor), and abbreviated IDE requirements as per 21 CFR 812.2(b) must be followed, along with informed consent requirements as per 45 CFR 46 and 21 CFR 50 and 56. These studies are subject to abbreviated regulatory requirements as per FDA.

Humanitarian Use Device (HUD): In order to qualify for HUD, both the IRB and the FDA must approve the device as such, and a Humanitarian Device Exemption (HDE) must be issued by the FDA. In this category, the effectiveness of the device does not need to be demonstrated; however the IRB must verify that the device does not pose unreasonable risk of injury or illness to the recipient in light of other available treatments, and the probable benefit of the device outweighs the risk of injury or illness and/or alternative treatment(s). HUD use must be consistent with current labeling of the device and for the FDA-approved indication. HUD devices must be labeled as such, and the labeling must state that although authorized by Federal Law, its effectiveness has not been demonstrated. Requirements for informed consent apply. To ensure additional protections, the IRB may impose more stringent restrictions for use of the HUD, such as re-review more frequently than annual or reporting on patients accrued. FDA approval must be obtained prior to IRB submission for this pathway.

2.3 Investigator and Investigator-Sponsor Responsibilities

At the time of IRB approval, investigators (and investigator-sponsors) will receive a copy of this SOP, which contains an outline of responsibilities and the applicable regulations. Regardless of device determination, all Principal Investigators must comply with applicable record keeping, labeling, monitoring and reporting. If the investigator is also the sponsor, there are additional responsibilities that are required (see Section **2.4** below). Per the FDA regulations, a Principal Investigator is a "Clinical Investigator" qualified by training and experience.

Note that individual sponsors may have additional requirements; it is the Principal Investigator's responsibility to ensure compliance with any additional sponsor requirements as well as to be

familiar with the full FDA, IRB and other regulatory requirements. Both investigators and investigator-sponsors should refer to 21 CFR Parts 11, 50, 54, 56 and 812 for a comprehensive listing of FDA requirements for the conduct of device studies.

All device principal investigators, regardless of device determination, must comply with the following:

1. Reporting to the sponsor (if applicable) and/or IRB:
    - Unanticipated adverse device effects
    - Withdrawal of IRB approval
    - Deviations from the approved investigational plan
    - Progress reports (minimum of annually) and a final report
    - Any other reports requested by the IRB and/or sponsor

All device principal investigators must also:

- Sign an agreement that includes a statement of the clinical investigator's commitment to: [21 CFR §812.43(c)(4)]
- Conduct the investigation in accordance with the agreement, the investigational plan, applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA
- Supervise all testing of the device involving human participants
- Ensure that the requirements for obtaining informed consent are met

While the principal investigator may delegate certain study-related tasks, any delegation of study-related tasks must be appropriate for the qualifications of those involved, and documented adequate training must be provided to delegates on how to perform such tasks.

All devices for a study must be stored in a locked environment under secure control with limited access. The area must be within an area of the principal investigator's control. Proper instructions on the use of the device must be provided to the subjects. A log must be kept regarding the receipt, use, and/or dispensing of the device (identification/serial number of the device, name of subject, date dispensed, by whom it was dispensed, and amount remaining) as well as the disposition of used and unused devices at the conclusion of the investigation. Details: [21 CFR §812.140]

The device Principal Investigator will maintain records of each participant's case history and exposure to the device. Case histories include the case report forms and supporting data (e.g., signed and dated consent forms and applicable records. Such records will include all relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each participant upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests as applicable to the study. A record of the exposure of each participant to the investigational device, including the date and time of each use, and any other interventions is required.

Study files must contain a record of the protocol, with documents showing the dates of and reasons for each deviation from the protocol, amendments and changes and IRB approval of each, current curriculum vitae (CV) of the Principal Investigator and those co-investigators who are engaged in the

research, GCP and human subjects training, any licensure applicable to the conduct of the research (ie: medical licensure), records of receipt and/or disposition of the device.

Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation must be maintained by the Principal Investigator.

2.4 Additional Responsibilities for Sponsor-Investigators

A sponsor-investigator for an IDE protocol must follow the FDA regulations in 21 CFR 812 applicable to sponsor responsibilities, particularly Subpart C. This includes:

- Obtain from each participating investigator a signed agreement that includes the investigator's CV, a statement of the investigator's relevant experience with dates (usually on the CV), a statement of any terminations of investigations or other research with an explanation, a statement of commitment to conduct the investigation in accordance with the protocol, investigational plan and regulations of the FDA as well as conditions of approval imposed by the IRB
- The record keeping requirements of 21 CFR 812.140(b)
- The monitoring requirements of 21 CFR 812.43(d)
- The required notification under 21 CFR 812.150(b)(1) to the FDA an all participating investigators of any evaluation of an unanticipated device effect within 10 days of first receiving notice of the effect

JUSTIFICATION FOR THIS SOP

21 CFR 807 (Establishment Registration & Device Listing for Manufacturers & Initial Importers Of Devices)

21 CFR 812 (Investigational Device Exemptions)

21 CFR 814 (Premarket Approval of Medical Devices)

21 CFR 820 (Quality System Regulation)

21 CFR 860 (Medical Device Classification Procedures)

21 CFR 54 (Financial Disclosure by Clinical Investigators)

21 CFR 56 (Institutional Review Boards)

21 CFR 11 (Electronic Records & Electronic Signature)

Federal Food, Drug and Cosmetic Act (21 USC 321(h))

FDA's Guidance for Industry: Investigator Responsibilities

FDA's Product Code Classification Database