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SOP 8.02 - FDA Regulated Medical Devices

1. Objective

To describe procedures for determining that a study is subject to FDA device regulations; procedures for determining whether a device used in a study is Investigational Device Exemption (IDE) exempt, subject to abbreviated IDE requirements, or subject to full IDE requirements; and procedures for the IRB making Significant Risk and Non-Significant Risk determinations.

2. General Description

Research studies intending to evaluate the safety and/or effectiveness of an investigational medical device must be conducted in compliance with 21 CFR 812. The IRB is responsible for verifying that studies involving investigational devices have a valid Investigational Device Exemption (IDE) issued by the FDA, qualify for an IDE exemption, or qualify for an abbreviated IDE. When an IDE is required, the IRB must make a Significant Risk/Non-Significant Risk determination regarding the device, unless this determination has already been made by the FDA.

Definitions

Device - Per Section 201(h) of the Food, Drug, and Cosmetic Act, a device is:

> An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:
>
> 1. recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
> 2. intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
> 3. intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and
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> which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

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

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

Investigational Device Exemption (IDE) - An IDE permits a device that otherwise would be required to comply with a performance standard or to have a premarket approval to be shipped lawfully for the purpose of conducting investigations, to collect safety and effectiveness data.

Investigator - an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

Noninvasive - when applied to a diagnostic device or procedure, means one that does not by design or intention:

1. Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or
2. Enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os. For purposes of this part, blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for noninvestigational purposes is also considered noninvasive.

Non-Significant Risk (NSR) Device - an investigational device that **does not** meet the definition of a Significant Risk (SR) device (see below).

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;
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;
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.

Sponsor - a person who initiates, but who does not actually conduct, the investigation, that is, the investigational device is administered, dispensed, or used under the immediate direction of another individual. 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 - an individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used. The term does not include any person other than an individual. The obligations of a sponsor-investigator under this part include those of an investigator and those of a sponsor.

Subject - a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease.

3. Roles & Responsibilities (Heading 1)

Execution of SOP: Principal Investigator (PI)/Study Personnel (SP), Office of Research Integrity – Human Subjects (ORI-HS) Staff, IRB Members

IRB Responsibilities

The IRB is responsible for determining whether a test article meets the definition of a device, as well as determining whether the device is exempt from IDE requirements, subject to abbreviated IDE requirements, or subject to full IDE requirements. The IRB is also tasked with making device risk determinations (Significant Risk or Non-Significant Risk).

The IRB is additionally responsible for reviewing device studies according to FDA regulations for the protection of human subjects (21 CFR 50 and 21 CFR 56).

Sponsor Responsibilities

Sponsors of a device investigation, as defined above, are responsible for selecting qualified investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring that IRB review and approval are obtained, submitting an IDE application to FDA, and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation. More information can be found at 21 CFR 812 Subpart C, and on the FDA's IDE Responsibilities webpage.

Investigator Responsibilities

An investigator, as defined above, is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with the requirements at 21 CFR 50. More information can be found at 21 CFR 812 Subpart E, and on the FDA's IDE Responsibilities webpage.

Sponsor-Investigator Responsibilities

A sponsor-investigator, as defined above, has the responsibilities of both the sponsor and the investigator.

4. Procedures

In addition to complying with the requirements of 21 CFR 50 and 21 CFR 56, all studies designed to test the safety and/or effectiveness of an investigational device must be conducted according to 21 CFR 812. When conducting a study designed to test safety and/or effectiveness of an investigational device, the IRB must determine which of the following applies to the proposed study:

1. The investigational device qualifies for one of the exemption categories identified in 21 CFR 812.2(c)
2. The study meets the abbreviated IDE requirements identified in 21 CFR 812.2(b); or
3. The study is conducted under a valid IDE issued by the FDA

Investigations Exempt from the IDE Requirements

An investigation may be exempt from the IDE requirements under 21 CFR 812 if the investigational device falls into one of the specified categories of exemption. This means that the IDE requirements are not applicable to the study.

The study sponsor/sponsor-investigator is responsible for making the initial determination about whether an investigational device meets the criteria for IDE exemption. The IRB may disagree and make a different determination. If the sponsor/sponsor-investigator believes a device to be exempt from the IDE requirements, the sponsor/sponsor-investigator provides the IRB with an explanation of its determination and any other information or documentation that may assist the IRB in making its own determination.

The following categories of devices are exempt from the IDE requirements:

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.
   In lay terms, this means a device that is currently legally-marketed and which is being used in accordance with its labeling.
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
   In lay terms, this means a device that is currently legally-marketed and which is being used in accordance with its labeling.
3. A diagnostic device, if the sponsor complies with applicable requirements in 809.10(c) and if the testing:
   a. Is noninvasive (see definition above)

b. Does not require an invasive sampling procedure that presents significant risk
c. Does not by design or intention introduce energy into a subject; and
d. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure

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.
5. A device intended solely for veterinary use
6. A device shipped solely for research on or with laboratory animals and is labeled in accordance with 812.5(c)
7. A custom device, as defined in 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution

Abbreviated IDE Requirements (Non-Significant Risk Device)

The FDA considers an investigational device to have an approved application for an abbreviated IDE when a device is determined to be a Non-Significant Risk (NSR) device that is not banned, and the sponsor complies with the following requirements:

1. Labels the device in accordance with 812.5
2. Obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a Significant Risk (SR) device, and maintains such approval
3. Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent (as required in 21 CFR 50) and documents it, unless documentation is waived by an IRB under 56.109(c).
4. Complies with the requirements of 812.46 regarding monitoring of investigations
5. Maintains applicable required records, and makes applicable required reports to the FDA.
   Specifically, the sponsor/sponsor-investigator must maintain the records required under 812.140(b) (4) and (5) and makes the reports required under 812.150(b) (1) through (3) and (5) through (10);
6. Ensures that participating investigators likewise maintain applicable required records, and make applicable required reports to the sponsor
   Specifically, the sponsor/sponsor-investigator must maintain the records required by 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7);
7. Complies with prohibitions against promotion and other practices (as detailed in 812.7)

The Principal Investigator (PI) or sponsor should provide the IRB with a device risk assessment and the rationale used to make the determination. If the IRB agrees that the device is an NSR, non-banned device, the study may proceed following IRB approval. Submission to and approval from the FDA is not required for NSR devices.

The IRB's responsibilities and procedures for making SR/NSR determinations are outlined below.

Investigational Device Exemption (IDE) Requirements for Significant Risk (SR) Devices

When an investigational device meets neither the exemption criteria nor the abbreviated IDE requirements, the study may only be approved when the FDA has issued an Investigational Device Exemption (IDE).

Investigators who submit for IRB review prior to submitting to the FDA for an IDE will generally be asked to withdraw their IRB submission and resubmit only after the IDE has been issued by the FDA.

An IDE is considered approved 30 days after the FDA receives the application, although an earlier notice of approval may be issued. While the sponsor/sponsor-investigator is responsible for determining if an IDE should be obtained

from the FDA, the IRB is responsible for verifying that an IDE number is valid for the proposed research study. More information on the IDE application process can be found on the FDA's IDE approval process website.

At least one of the following documents should be included in the information provided to the IRB, to serve as verification of an IDE:

- A study protocol, as submitted to the FDA, including an IDE number
- Communication from the FDA with verification of the IDE number
- When the IDE is held by a sponsor:
  - A sponsor's protocol specifying the IDE number
  - Communication from the sponsor verifying the IDE number

Significant Risk (SR) and Non-Significant Risk (NSR) Distinction

The main difference between SR and NSR devices is that NSR devices have fewer regulatory requirements than SR devices. NSR devices can follow abbreviated IDE requirements, whereas SR devices must follow the full IDE requirements.

The practical effect of this distinction is that, once IRB approval is secured for an NSR device study, the study may begin at the institution immediately, without notification to the FDA. The FDA is usually not informed of the existence of approved NSR devices because sponsors and IRBs are not required to report NSR device approvals to the FDA.

If the IRB believes a device is SR, then the investigation may not begin until both the IRB and the FDA approve the investigation.

The process for the IRB making SR/NSR determinations is described in the next section. The SR/NSR decision by the IRB is important to the FDA because the IRB serves as the FDA's surrogate with respect to review and approval of NSR devices for use in research

Making the SR/NSR Determination

The process for making an SR/NSR determination for a device study follows the same general process:

1. Initial assessment from sponsor/sponsor-investigator
2. IRB assessment of relevant information
3. Final determination made by the IRB
4. Ultimate authority for the determination lies with the FDA

Initial Assessment

The sponsor/sponsor-investigator makes the initial assessment of device risk, categorizing the device as either Significant Risk (SR) or Non-Significant Risk (NSR). If the sponsor/sponsor-investigator considers a device study to be NSR, the sponsor/sponsor-investigator provides the IRB with an explanation of its determination and any other information that may assist the IRB in evaluating the risk of the device.

IRB Assessment of Relevant Information

In making its own assessment of device risk, the IRB may use several different types of information or documentation. Such information/documentation may include:

- A description of the device
- Reports of prior investigations with the device
- The proposed investigational plan
- Description of patient selection criteria
- Monitoring plan
- FDA's assessment of device risk, if such an assessment has been made

If the FDA has made its own assessment of the device's risk, the sponsor/sponsor-investigator must inform the IRB of this assessment. If requested by the IRB, the sponsor/sponsor-investigator should inform the IRB whether any other

IRBs have reviewed the proposed study and what device risk determination was made by them. The IRB may also consult with the FDA in order to make this determination.

IRB's Final Determination

The IRB must either agree or disagree with the sponsor/sponsor-investigator's initial SR/NSR assessment. If the IRB agrees with the sponsor/sponsor-investigator's NSR assessment, and approves the study, then the NSR device study may begin without submission of an IDE application to the FDA.

If the IRB disagrees with the sponsor/sponsor-investigator's NSR assessment, the IRB must notify the investigator. Additionally, the sponsor should notify the FDA that an SR determination has been made. The study can only proceed following FDA approval of an IDE application. The sponsor/sponsor-investigator, not the IRB, is responsible for the IDE application process.

Some consideration the IRB should make during a device risk assessment include:

- The risk determination is based on the proposed use of a device in an investigation, and not on the device alone. Device investigations which introduce risk through other research-related activities should be considered in the risk determination.
- Consider the nature of the potential harm that may result from the use of the device. SR studies are those that present a potential for serious risk to the health, safety, or welfare of a subject. Studies where the potential harm to subjects could be life threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure should be considered SR
- Consider whether the subjects will need to undergo an additional procedure as part of the investigational study, for example, a surgical procedure. IRBs should consider the potential harm the procedure could cause as well as the potential harm caused by the device.
- **NSR determination and IRB use of the phrase "minimal risk." NSR determinations relate solely to the risk of the device. Whereas the IRB uses "minimal risk" to describe the overall study risk level, which can be minimal risk or greater than minimal risk. When reviewing a device study, an IRB must make both a device risk determination (SR vs NSR) and an overall study risk determination (minimal risk vs. greater than minimal risk).** NSR devices can still be used in greater than minimal risk research. Even when NSR devices are used in a study that is minimal risk, full board review will be required. This is because the expedited category for devices only allows for the use of devices that do not require an IDE. Since NSR devices do require an IDE (albeit, an abbreviated one), the use of an NSR device in a minimal risk research study will not be able to qualify for expedited review under Category 1.

The IRB must document the SR/NSR determinations in the meeting minutes. The documentation should include the rationale used by the IRB to make the SR/NSR determination.

Ultimate Authority

The FDA has the ultimate decision in determining if a device is SR or NSR. If the FDA has made its own determination regarding a device, this determination is final. If the FDA does not agree with an IRB's determination that a device is NSR, then the device is considered SR and an IDE application must be submitted to the FDA.

IRB Responsibilities Following SR/NSR Device Determinations

The IRB has responsibilities following its determination of device risk. These responsibilities vary depending on whether the device is SR or NSR.

SR Device Determination

If the IRB decides the study involves an SR device, the following actions must be taken by the IRB:

1. The IRB must document in its minutes the determination of SR and the rationale

2. The IRB must notify the investigator and, where appropriate, the sponsor, of the SR determination
3. The IRB must proceed to review the study, applying the criteria for approval outlined in 21 CFR 56.111

NSR Device Determination

If the IRB decides the study involves an NSR device, the following actions must be taken by the IRB:

1. The IRB must document in its minutes the determination of NSR and the rationale
2. The IRB must proceed to review the study, applying the criteria for approval outlined in 21 CFR 56.111

The IRB Decision to Approve or Disapprove the Research

Once a device has been determine to either be exempt from the IDE requirements, or determined to be SR or NSR, the IRB must then consider the study as a whole, and determine whether the study can be approved. The criteria for approval outlined in 21 CFR 56.111 will be applied to the study, just as in any other FDA-regulated study.

This includes making an overall risk determination for the study as a whole. This risk determination will differ from the SR/NSR determination, which is based solely on the seriousness of harm that could result from the device itself. The overall study risk determination (minimal risk vs. greater than minimal risk) is based on the study activities as a whole, including the use of the device.

The FDA considers all SR device studies to present greater than minimal risk, meaning full board review is required for all SR device studies. Some NSR studies may qualify as minimal risk; however, because the device is considered to have an IDE (albeit, an abbreviated one), the study will not qualify for expedited review under Expedited Category 1.

Software and Mobile Medical Applications

Some software functions or applications (mobile or not) can be considered medical devices. A software function or application is considered a medical device when the software function/application otherwise meets the definition of a medical device. Examples include:

- Software functions and applications that are accessories to currently-regulated medical devices (ex: software that controls inflation and deflation of a blood pressure cuff)
- Software functions and applications that transform a mobile device into a medical device (ex: ann attachment of a blood glucose strip reader to a mobile platform which then functions as a blood glucose monitor)
- Software functions and applications that perform patient-specific analysis and provide patient-specific diagnosis or treatment recommendations, and which present a higher level of risk to patients if the software/application does not perform as intended (ex: software functions that use patient-specific parameters to create a dosage plan for radiation therapy)

However, some software functions/applications that do meet the definition of a medical device fall under the FDA's "enforcement discretion," meaning that the FDA chooses not to apply the IDE requirements to these types of software functions/applications. The decision of whether a software function/application is under FDA oversight depends primarily on the software function's/application's risk to the public.

Examples of software functions/applications that are or are not subject to FDA regulations for devices can be found in the FDA's guidance on mobile medical applications.

If the IRB determines that a software function/application does not fall under enforcement discretion, then the PI and IRB must follow the procedures outlined above for medical devices. If the IRB determines that a software function/application does fall under enforcement discretion, then the procedures for devices that are IDE exempt must be followed.

5. References

21 CFR 50
21 CFR 56

21 CFR 812
FDA Frequently Asked Questions about Medical Devices
FDA Frequently Asked Questions on In Vitro Diagnostic (IVD) Devices
FDA Guidance on Mobile Medical Applications
FDA Guidance on Significant Risk and Nonsignificant Risk Medical Device Studies
FDA IDE Approvals Process website
FDA IDE Responsibilities website