Guidance: Significant vs Nonsignificant Risk Devices

Overview

The FDA Regulations define an investigational device as a device, including a transitional device that is the object of an investigation. The regulations describe three types of device studies:

(i) Significant Risk (SR)
(ii) Non-Significant Risk (NSR)
(iii) Exempt

This guidance is a summary of two FDA documents: Frequently Asked Questions About Medical Devices and Significant Risk and Nonsignificant Risk Medical Device Studies - Information Sheet

Note: Sponsors are responsible for making the initial risk determination and presenting it to the IRB. If there is no external funding source for the study, the PI is considered the Sponsor.

Significant Risk (SR) device

Under the regulations, a SR device means an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is purported or represented to be for use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Is for the 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
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Significant risk device studies must:

- Follow all the IDE regulations at 21 CFR 812.
- Have an IDE application approved by FDA before they may proceed.

Examples: Artificial skin and interactive wound and burn dressings, intravascular stents, bronchial tubes. See the FDA info sheet for more examples.

Sponsor's responsibilities

- The sponsor should provide the IRB with a risk assessment and the rationale used in making its SR determination.
- The sponsor must submit an IDE application to the FDA and obtain the agency's approval of the study.
- The sponsor must advise its clinical investigators about the SR status and obtain their agreement to comply with the applicable regulations governing such studies.
- Sponsors should provide the IDE number and/or a copy of the IDE approval letter to the IRB when requested.
- Sponsors may send their SR device study to an IRB for review before the IDE application is approved by the FDA. However, the FDA cautions that an SR device study may not begin until the FDA approves the IDE.

Non-Significant Risk (NSR) device

Devices that do not fall under the definition of SR are considered NSR devices.

- Non-significant device studies must follow the abbreviated IDE requirements at 21 CFR 812.2(b). These abbreviated requirements address labeling, IRB approval, informed consent, monitoring, records, reports, and the prohibition against promotion. However, there is no need to make progress reports or final reports to FDA.
- NSR device studies do not have to have an IDE application approved by the FDA.
- Sponsors and IRBs do not have to report the IRB approval of an NSR device study to the FDA. This means that an IRB may approve an NSR device study and an investigator may conduct the study without the FDA knowing about it.
- An IRB's NSR determination is important because the IRB serves as the FDA's surrogate for review, approval, and continuing review of the NSR device studies.
- An NSR device study may start at the institution as soon as the IRB reviews and approves the study without prior approval by the FDA.

Examples: Low-power lasers for the treatment of pain and daily-wear contact lenses. See the FDA info sheet for more examples.

Sponsor's responsibilities

- The sponsor should provide the IRB with a risk assessment and the rationale used in making its NSR determination.
- If the sponsor identifies a study as NSR, the sponsor must provide the reviewing IRB an explanation of its determination and should provide any other information that may help the IRB in evaluating the risk of the study. For example, a description of the device,

reports of prior investigations with the device, the proposed investigational plan, subject selection criteria, and other information the IRB may need.

- If FDA has determined that the study is NSR, the sponsor should inform the IRB. By providing such risk determination information to the IRB, the IRB's workload should be reduced and the review process should be facilitated.

Exempt devices

For studies that are exempt from the IDE regulations, the IRB does not need to decide whether the study poses a significant risk or nonsignificant risk. However, the IRB must still review the study according to the IRB regulations before the investigation may begin.

Examples:

- Consumer preference testing, testing of a device modification, or testing of two or more devices in commercial distribution if the testing does not collect safety or effectiveness data, or puts subjects at risk.
- Studies of an already cleared medical device in which the device is used or investigated by the indications in the cleared labeling are exempt from Part 812.5.
- Premarket-approved device if the device is being studied for the indications in the approved labeling
- Diagnostic device studies (e.g., in vitro diagnostic studies) are exempt from the requirements of 21 CFR Part 812 under certain circumstances. The study is exempt as long as the sponsor complies with the requirements at 21 CFR 809.10(c) for labeling, and if the testing: (i) is noninvasive; (ii) does not require an invasive sampling procedure that presents significant risk; (iii) does not by design or intention introduce energy into a subject; and (iv) is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure. 21 CFR 812.2(c)(3).

Who determines a device study as SR or NSR?

Sponsors are responsible for making the initial risk determination and presenting it to the IRB.

Unless the FDA has already made a risk determination for the study, the IRB must review the sponsor's SR or NSR determination for every investigational medical device study reviewed and modify the determination if the IRB disagrees with the sponsor. If FDA has already made the SR or NSR determination for the study, the agency's determination is final.

FDA is the final arbiter as to whether a device study is SR or NSR and makes the determination when an IDE is submitted to the FDA or if asked by the sponsor, clinical investigator, or IRB.

Note: The FDA is available to help the sponsor, clinical investigator, and the IRB when making its risk determination.

IRB responsibilities

- An Institutional Review Board (IRB) evaluates the potential risks of a device during a convened meeting. In the protocol, it is important to include a detailed description of the device, a risk assessment, any prior investigations conducted with the device, the proposed investigational plan, and the criteria used to select subjects.

- The IRB must make two separate decisions, based on different criteria.
  1. Is the investigation approvable or not?
     - The criteria for deciding if a study involving either an SR or NSR device can be approved are the same as those used to evaluate any proposed research project.
  2. Does the device present SR or NSR?
     - The IRB review criteria and review process are described below.

- If the investigator or sponsor believes a device poses NSR, this should be well explained in the IRB protocol application form. The IRB should also be informed if the FDA or any other IRB has determined the device to present SR or NSR and provide any further information requested by the IRB.

- An IRB may approve the study as an SR device study, but the study may not begin until the FDA approves the sponsor's IDE application.

- To facilitate the IRB's review of the study, an IRB may ask the sponsor for proof (i.e., a copy of the FDA's approval or conditional approval letter) that an SR study has an FDA-approved IDE application.

- An IRB may agree or disagree with the sponsor's initial NSR assessment.
  - If the IRB agrees with the NSR determination, the study may be approved using the FDA approval criteria. The study may begin without submission of an IDE application to the FDA.
  - If the IRB disagrees with the NSR determination, and decides the device poses a significant risk, The study can only be conducted at this institution as a study involving an SR device. The investigator or sponsor must notify the FDA that an SR determination has been made for the device (whether or not the study is ultimately conducted at that institution). The study can be conducted as an SR investigation following FDA approval of an IDE application.

- Document the device risk determination: The IRB should write its decision in the meeting minutes. The minutes should describe the IRB's reason for its SR or NSR determination and may also include the documentation used to establish the IDE status for the study.
    - For an SR determination, such documentation may include, for example, a copy of the IDE approval or conditional approval letter from the FDA.
    - For an NSR determination, the documentation may include the FDA's NSR determination where the agency has made the determination. FDA will issue an NSR letter upon written request.

> Note: The FDA will issue an NSR letter upon written request.

What should IRBs consider when making a device risk determination?

What is the basis for the risk determination? The determination of significant risk depends on the use of the device in the particular study, as well as the inherent risks of the device itself.

What is the nature of the 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. Included among those devices that present SR are devices for which 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.

Will the subject need to undergo an additional procedure as part of the investigational study, for example, a surgical procedure? If the subject must undergo a procedure as part of the study, e.g., a surgical procedure to implant the device, the IRB must consider the potential harm caused by the procedure, as well as the potential harm caused by the device.

Difference between NSR and Minimal Risk Determinations: The responsibility to make an SR/NSR determination for a device study and the concept of "minimal risk require separate determinations. "Minimal Risk" is a term used in the IRB regulations in part to identify certain studies that IRBs may approve through an expedited review procedure. For a device study to be eligible for expedited review, it must be an NSR study AND present no more than minimal risk to the subject.

Difference Between SR/NSR Determinations and Approval Decisions: The judgment about whether a study poses a significant risk or nonsignificant risk is based on the significance of the potential harm that may result from participation in the study, including the use of the device; whereas the IRB's decision to approve a study for implementation is based on the study's risk-benefit assessment.

Several examples when determining device risks:

Example 1: A pacemaker that is a modification of a commercially available pacemaker poses SR because the use of any pacemaker presents a potential for serious harm to the subjects. This is true even though the modified pacemaker may pose less risk, or only slightly greater risk, in comparison to the commercially available model. The degree of possibly reduced or increased risk associated with the investigational pacemaker should only be considered (about possible decreased or increased benefits) when assessing the approval of the study.
Example #2: An extended-wear contact lens is considered SR because wearing the lens continuously for 30 days presents a potential for injuries not normally seen with daily-wear lenses, which are considered NSR.
Example #3: n investigational study of a sensor pad to find out if the device can detect the electrical activity of the spinal cord may be NSR, if the study of the sensor pad takes place at the same time as the planned surgical repair of the spinal cord, if all the following are true:

- repair of the spinal cord would occur anyway;
- the sensor pad does not present a potential for serious risk to the health, safety, or welfare of a subject (for example, placing the pad would not prolong or interfere with the operation);
- the sensor pad is not implanted;
- the pad is not of substantial importance in diagnosing, curing, mitigating, or treating disease.

The FDA may overrule an IRB's determination

The FDA has the ultimate decision in determining if a device is SR or NSR. On some occasions, the FDA may overrule the IRB's decision that a device presents NSR or SR. When the FDA overrules an IRB's NSR determination, an IDE application must be submitted to the FDA.
On the other hand, when the FDA considers the device to be NSR, the FDA may return an IDE application to the investigator or sponsor. The IRB must then determine if it wants the study to take place at this institution as an NSR device investigation.

References

Federal Regulations

Significant Risk and Nonsignificant Risk Medical Device Studies - Information Sheet (fda.gov)

Frequently Asked Questions About Medical Devices