SIGNIFICANT RISK OR NON-SIGNIFICANT RISK DEVICE DETERMINATIONS BY THE DUHS IRB

12/3/2024

The Investigational Device Exemption (IDE) regulations [21 CFR part 812] describe two types of device studies, "significant risk" (*SR*) and "nonsignificant risk" (*NSR*).

- **Significant Risk (SR) Device**
  Under 21 CFR 812.3(m), an 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; or
  - 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; or
  - 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
  - otherwise, presents a potential for serious risk to the health, safety, or welfare of a subject.

- **Nonsignificant Risk (NSR) Device**
  An NSR device study is one that does not meet the definition for an SR device study.

The SR/NSR determination is based on the proposed use of a device in the research study, and not on the device alone. The IRB must also consider the potential harm of any additional procedure(s) needed as part of the research to study the device, as well as the potential harm caused by the device itself.

The FDA Information Sheet Guidance on Significant Risk and Nonsignificant Risk Medical Device Studies (Jan 2006) has a list of commonly studied medical devices that may be helpful in making SR and NSR determinations. This can be found at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/significant-risk-and-nonsignificant-risk-medical-device-studies.

For information on device studies that are **exempt** from the IDE regulation, see the DUHS IRB Checklist titled “Checklist to Determine if an Investigational Device Exemption (IDE) is Required Where an IDE is not Provided” found at https://irb.duhs.duke.edu/principal-investigator-checklists, and the FDA Information Sheet Guidance entitled, “Frequently Asked Questions About

Medical Devices" at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/frequently-asked-questions-about-medical-devices.

If an exempt study is being conducted to collect data to support either a clinical investigation or a marketing application, then the study must comply with 21 CFR Part 50 and 21 CFR Part 56. For device studies that are exempt from the IDE regulations, the IRB does not need to decide whether the device poses a significant risk or nonsignificant risk. However, IRB approval is still required before the investigation may begin.

SPONSOR/INVESTIGATOR RESPONSIBILITIES

Sponsors are responsible for making the initial risk determination and presenting it to the IRB. FDA is also available to help the sponsor, clinical investigator, and IRB in making the risk determination.

When a Duke PI is the regulatory sponsor (e.g. person who initiates the investigation), they may work with the Office of Regulatory Affairs and Quality (ORAQ) to obtain FDA feedback on the risk level of the study and provide the FDA feedback to the IRB. ORAQ can work with study teams to submit either a formal Study Risk Determination, under FDA's Q-Submission Program, or an IDE to FDA.

Per the January 2006 Guidance, "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 FDA or if asked by the sponsor, clinical investigator, or IRB." With this in mind, it is DUHS IRB policy not to make a definitive significant risk determination if the IRB disagrees with an NSR determination, but to request that the study team obtain feedback from FDA regarding whether an IDE application (SR) is required.

IRB will direct the study team to work with ORAQ to obtain a risk determination from FDA. ORAQ can be contacted by email at ORAQ@dm.duke.edu.

IRB RESPONSIBILITIES

Unless 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 (as above) 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.

IRBs do not have to make the SR or NSR determination if FDA has already made the risk determination. Most often, clinical investigators submit SR device investigations for IRB review after the study has already received IDE approval from FDA. If the device already has an approved IDE application, the IRB will require documentation from the sponsor that the IDE number applies to the device to be used for the study under consideration. This may be reflected in the sponsor's protocol, or correspondence from the sponsor or FDA. FDA will provide a written determination of SR/NSR status at the request of the IRB.

For studies without a documented IDE, the DUHS IRB will make the SR or NSR determination about a device study by reviewing relevant information at a convened meeting (for IRB considerations when making the SR/NSR determination, see next section below). If the IRB determines the device, as used in the research study, is NSR, the IRB may approve the study using the criteria at 21 CFR 56.111. In that case, no submission of an IDE application to FDA is needed.

If the IRB determines that FDA feedback is required for the risk determination, the IRB will tell the clinical investigator within the study modifications. Study teams should reach out to ORAQ (ORAQ@dm.duke.edu) to obtain FDA feedback on the risk level of the device as used within the study. ORAQ can assist the team to submit either a formal Study Risk Determination or an IDE.

The device determination of the IRB will be documented in the meeting minutes and the study sponsor and/or study team will be notified of its obligations under the applicable part of 21 CFR 812.

IRB CONSIDERATIONS WHEN MAKING THE SR/NSR DETERMINATION

The DUHS IRB will consider the following in determining whether a device study poses a SR or NSR:

- the sponsor's description of why the study is not SR.
- whether the proposed NSR device study meets the definition of "significant risk" (see definition above).
- the proposed use of the device in the research study, as well as any protocol related procedures and tests, not just the device (test article) alone. (This process is different from the IRB review process found at 21 CFR 56.111(a)(2)).
- the nature of the harm that could potentially result from use of the device in the intended population.
- additional information from the sponsor, if needed.

DISTINCTIONS BETWEEN SR/NSR DETERMINATIONS AND MINIMAL RISK DETERMINATIONS

IRB members and staff should not confuse their responsibility to make an SR/NSR determination for a device study with the concept of "minimal risk." The term "Minimal Risk" is a Common Rule definition (45 CFR 46) in part to identify certain studies that the IRB may approve through an expedited review procedure.

SR/NSR determinations are based on the FDA definitions under 21 CFR 812 and are separate and distinct from Greater than Minimal Risk/Not Greater than Minimal Risk determinations under the Common Rule.

It is a DUHS IRB policy that NSR determinations are made at a convened board meeting. For a device study to be eligible for subsequent expedited review, it must involve the use of an NSR device AND the research must present no

greater than minimal risk to the subject (21 CFR 56.110). Upon making its initial determination that a proposed device study is NSR, and that the study is "minimal risk," the convened board may vote to expedite the study under expedited Category 1 at the time of continuing review the following year, assuming no change in risk level in the interim. It is also permissible to indicate Category 9 in iRIS to indicate that initial full board review did occur. Note that device studies that meet IDE exemption criteria and are no greater than minimal risk do not require review by a convened board.

For a significant risk device study, the research will always involve more than minimal risk. However, a non-significant risk device study may, for reasons other than those related to the device portion of the study, also involve more than minimal risk.

MAJOR DIFFERENCES BETWEEN SR AND NSR DEVICE STUDIES

The major differences between SR and NSR studies are in the IDE approval process and in the sponsor's record keeping and reporting requirements.

1. Significant Risk (SR) Device Studies

- SR device studies must have an IDE application approved by FDA before they may proceed or have written documentation from the FDA Center (CDRH or CBER) that a separate IDE application is not needed because the study data will be submitted under an IND application.
- SR device studies must follow all applicable IDE regulations at 21 CFR 812 (even if conducted under an IND application).

2. Nonsignificant Risk (NSR) Device Studies

- NSR device studies must follow the abbreviated requirements at 21 CFR 812.2(b).
- These abbreviated requirements address labeling, IRB approval, informed consent, monitoring, records, reports, and 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 FDA.
- Sponsors and IRBs do not have to report the IRB approval of an NSR device study to FDA. Thus the 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 DUHS as soon as the DUHS HRPP reviews and approves the study and without prior approval by FDA.

Previous Version(s): 7/25/2008, 5/25/2013, 11/3/2015, 3/4/2016, 3/25/2021