

**SEATTLE CHILDREN'S RESEARCH INSTITUTE  
OPERATING POLICIES / PROCEDURES**

<b>DEPARTMENT:</b>	Institutional Review Board
<b>POLICY NUMBER:</b>	IRB-041
<b>REPLACES:</b>	New Policy
<b>EFFECTIVE DATE:</b>	February 09, 2010
<b>REVISION DATE:</b>	

**TITLE:** Significant/Nonsignificant Risk Determinations for Investigational Devices

**SUMMARY:**

When a clinical investigation is conducted to determine the safety and effectiveness of a device, the first step is to determine whether the device can be exempt from the IDE requirements. If a clinical investigation of a device is not exempt from the IDE requirements, the appropriate risk category must be determined. The risk determination will be based on the proposed use of a device in an investigation, and not on the device alone. Seattle Children's IRB follows this policy/procedure regarding significant/nonsignificant risk determinations for investigational device use.

**POLICY/PROCEDURE:****Definitions**

Clinical Investigation: Any experiment that involves a test article (here, a medical device for human use) and one or more human subjects and that either is subject to requirements for prior submission to the FDA under section 505(i) (new drug application) or 520(g) (new device application) of the Act, or is not subject to requirements for prior submission to the FDA under these sections of the Act, but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

Investigational Device Exemption (IDE): An investigational device exemption (IDE) allows an investigational (unapproved) device to be used in a clinical 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 FDA. 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.

The FDA Investigational Device Exemptions regulation (21 CFR 812) describes three types of device studies: significant risk (SR), nonsignificant risk (NSR), and exempt studies.

Clinical studies with devices of significant risk must be approved by FDA and by an Institutional Review Board (IRB) before the study can begin. Studies involving devices of nonsignificant risk or devices that fit within an exemption category require only IRB approval before the study can begin.

## **041-1 Determining Whether a Device is Exempt**

041-1.1 When a clinical investigation is conducted to determine the safety and effectiveness of a device, the first step is to determine whether the device can be exempt from the IDE requirements. It is the sponsor's responsibility to provide sufficient justification to the IRB to support the exemption being claimed. The sponsor's explanation should include a reference to the relevant exemption category. There are seven possible categories for exemption (see section 812.2(c)):

041-1.1.1 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.

041-1.1.2 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 under subpart E of part 807 in determining substantial equivalence.

041-1.1.3 A diagnostic device, if the sponsor complies with applicable requirements in 809.10(c) and if the testing:

- a. Is noninvasive,
- 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.

041-1.1.4 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.
- 041-1.1.5 A device intended solely for veterinary use.
- 041-1.1.6 A device shipped solely for research on or with laboratory animals and labeled in accordance with 812.5(c).
- 041-1.1.7 A custom device as defined in 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

Categories reflected in 041-1.1.3 and 041-1.1.4 are the most commonly applied exemptions.

## 041-2 Distinguishing Between Significant Risk and Nonsignificant Risk Studies

041-2.1 If a clinical investigation of a device is not exempt from the IDE requirements, the appropriate risk category must be determined. The risk determination will be based on the proposed use of a device in an investigation, and not on the device alone. The following types of device studies must be considered:

041-2.1.1 Significant Risk Device (SR) 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 supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- 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.

041-2.1.2 Nonsignificant Risk Device (NSR): is a device that does not meet the definition for an SR device.

041-2.2 Process for determining the risk category:

040-2.2.1 **FDA**: If FDA has already made a SR or NSR determination for the study, the agency's determination is final. The sponsor should provide the IDE approval letter to the IRB for an SR study. If FDA has determined that the study is NSR, the sponsor should inform the IRB of the decision in writing.

- 041-2.2.2 **Sponsor:** If the FDA has not made a determination, sponsors are responsible for making an initial risk determination and providing the rationale in writing for the IRB.
- 041-2.2.3 **IRB:** 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 must modify the determination if the IRB disagrees with the sponsor. FDA is available to help the IRB when making its risk determination.

The FDA will make the ultimate decision in determining if a device study is SR or NSR. If the FDA does not agree with an IRB decision to identify a study as an NSR device study, an IDE application must be submitted to the FDA and the study must be presented again to the IRB as an SR investigation. If a sponsor files an IDE with the FDA because it is presumed to be an SR study, but the FDA classifies the device study as NSR, the FDA will return the IDE application to the sponsor and the study must be presented to the IRB as an NSR investigation.

### 041-3 Consequences of the Risk Determination

041-3.1 The major differences between SR and NSR studies are in the IDE approval process and in the sponsor's record keeping and reporting requirements, as outlined below:

SR Device Studies	NSR Device Studies
Must follow all the IDE regulations at 21 CFR 812	Must follow the <u>abbreviated</u> 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.
Must have an IDE application approved by FDA <u>before</u> the study may proceed.  If the IRB believes that a study is an SR device study, the investigation may not begin until both the IRB and the FDA approve the study.	Do <b>not</b> need to have an IDE application approved by FDA. IRB approval must be obtained before the investigation can begin.  Sponsors and IRBs do not have to report the IRB approval of an NSR device study to FDA. This means that an IRB may approve an NSR device study and an investigator may conduct

	<p>the study without FDA knowing about it.</p> <p>The IRB serves as the FDA's surrogate for review, approval, and continuing review of NSR device studies. When an NSR study is approved by an IRB, it is "deemed" to have an IDE without formal FDA approval.</p>
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#### 041-4 IRB Determinations

041-4.1 The Board will make the SR or NSR determination about a study by reviewing relevant information at a convened meeting. If the sponsor identifies a study as an NSR, the sponsor must provide the IRB with an explanation of its determination and any other information that may assist the IRB in evaluating the risk of the study. The sponsor is expected to provide the following information:

- description of the device;
- reports of prior investigations with the device;
- the proposed investigational plan;
- a description of patient selection criteria and monitoring procedures;
- any other information the IRB deems necessary to make its decision

041-4.2 In deciding if a study poses an SR, the IRB should consider the following issues:

- *What is the basis for the risk determination?* The risk determination is based on the proposed use of a device in an investigation, and not on the device alone.
- *What is the nature of harm that may result from use of the device?* SR studies are those that present a potential for serious risk to the health, safety, or welfare of a subject.
- *Will the subject need to undergo an additional procedure as part of the investigational study, for example, a surgical procedure?* The IRB should consider the potential harm the procedure could cause as well as the potential harm caused by the device.

#### 041-5 Documentation

- 041-5.1 The Seattle Children's IRB will document in the meeting minutes and in written correspondence to the investigator any determination that a device is a significant risk or nonsignificant risk device. The minutes will describe the IRB's reason for its SR or NSR determination and may also refer to the documentation used to establish the IDE status for the study.
- 041-5.2 If the IRB identifies the study as SR, the IRB will review the protocol, applying the requisite criteria (45 CFR 46.111; 21 CFR 56.111) and document its determinations, including the SR determination, in a letter to the investigator. The investigator will, in turn, notify the sponsor of the SR determination. An IDE will be obtained by the sponsor and submitted to the IRB.
- 041-5.3 If the IRB identifies the study as NSR, the IRB will proceed to review the study, applying the requisite criteria (45 CFR 46.111; 21 CFR 56.111). The IRB determination will be documented in written correspondence to the investigator. If the study is approved by the IRB, the sponsor and the investigator must comply with abbreviated IDE requirements (21 CFR 812.2(b)), and informed consent and IRB regulations (45 CFR 46; 21 CFR 50 and 56).

#### **041-6 IRB Approval or Disapproval of the Application**

- 041-6.1 Once the SR/NSR decision is reached, the IRB will consider whether or not the study should be approved. The criteria for deciding if SR and NSR studies should be approved are the same as those for any other study (45 CFR 46.111; 21 CFR 56.111).
- 041-6.2 If a device is classified as a significant risk device by the IRB and the sponsor has not obtained IDE approval from FDA at the time of initial review, the provision of the IDE number and FDA approval letter should be a contingency to final approval. The contingency should clarify that if the FDA determines the device should be classified as NSR, or requires additional changes prior to approval of the IDE, the application will require additional review by the convened IRB.
- 041-6.3 The minutes of IRB meetings will document whether a device has been determined to be a significant risk or nonsignificant risk device and the rationale for SR/NSR decisions, as well as the subsequent approval or disapproval decisions regarding the clinical investigation.
- 041-6.4 At the time of continuing review, the IRB may request additional documentation to be certain the investigator is following the IDE requirements. If the investigator holds the IDE for a significant risk device, a copy of the annual report to the FDA will be requested.

## 041-7 FDA Requirements for Sponsor-Investigators of New Devices

The following is an overview of the FDA requirements for sponsors with an Investigational Device Exemption (IDE). If an investigator is also the sponsor for a device, the following requirements must be met:

### 041-7.1 Major Responsibilities of Sponsors for Significant Risk Device Studies

Obtain FDA and IRB approval for IDE.	(21 CFR 812.42)
Select investigator(s) with appropriate training and experience.	(21 CFR 812.43)
Select a monitor in accordance with FDA regulations.	(21 CFR 812.43)
Ship investigational devices only to qualified investigators.	(21 CFR 812.43)
Maintain complete and accurate records documenting the financial interests of all participating clinical investigators, including sponsor payments.	(21 CFR 812.43) (21 CFR 54)
Supply the investigator(s) with copies of the investigational plan and copies of prior device investigations.	(21 CFR 812.45)
Ensure that investigator(s) are complying with FDA, IRB, and sponsor requirements.	(21 CFR 812.46)
Conduct an evaluation of unanticipated adverse events and terminate the study if necessary.	(21 CFR 812.46)
Resume terminated studies only after receiving approval from the FDA and IRB.	(21 CFR 812.46)
Maintain accurate and complete records in accordance with FDA regulations.	(21 CFR 812.140)
Provide required reports to IRB, investigator(s), and FDA in a timely manner.	(21 CFR 812.150)
Label the device in accordance with FDA requirements.	(21 CFR 812.5)
Promote the device in accordance with IRB and FDA requirements.	(21 CFR 812.7)
Comply with federal regulations regarding emergency use.	(21 CFR 812.47)
Ensure any electronic data and source documentation meets the same fundamental elements of data quality that are expected of paper records	(21 CFR 11)
Ensure the minimum current good manufacturing practice of devices in compliance with 21 CFR 820, Quality System Regulation	(21 CFR 820)

### 041-7.2 Major Responsibilities of Sponsors with Nonsignificant Risk Device Studies

Label the device in accordance with FDA requirements.	<b>21 CFR 812.5</b>
Obtain IRB approval of the investigation as a nonsignificant risk device study and maintain IRB approval during the investigation.	<b>21 CFR 812.2</b>
Ensure that each investigator obtains consent for each subject unless the IRB grants a waiver.	<b>21 CFR 812.2</b>
Comply with FDA requirements for monitoring the study. (See above for monitoring requirements.)	<b>21 CFR 812.46</b>
Maintain accurate and complete records in accordance with FDA regulations, and report the results to the FDA, IRB, and investigators.	<b>21 CFR 812.140 and 21 CFR 812.150</b>
Ensure that each investigator maintains accurate and complete records in accordance with FDA regulations and reports the results to the appropriate parties.	<b>21 CFR 812.140 and 21 CFR 812.150</b>
Obtain a signed agreement from the investigator(s) using the required FDA documents, including complete and accurate records documenting the financial interests of all participating clinical investigators, including sponsor payments	<b>21 CFR 812.43 21 CFR 54</b>
Ensure any electronic data and source documentation meets the same fundamental elements of data quality that are expected of paper records	<b>21 CFR 11</b>
Ensure the minimum current good manufacturing practice of devices in compliance with 21 CFR 820, Quality System Regulation	<b>21 CFR 820</b>
Promote the device in accordance with IRB and FDA requirements.	<b>21 CFR 812.7</b>

**Submitting Office:** Institutional Review Board

**Approved by:**

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