

A Framework for Device Classification for Clinical Research Protocols using MRI in the In Vivo NMR Center April 17, 2020

NIH has a long running MRI program where early research developments have been pioneered and translated into routine clinical application. At NIH In Vivo NMR Center, MRI is used both for clinical decision making, development of new imaging technology and for basic research. These studies rely on design of novel research pulse sequences and processing strategies. In addition, many MRI studies rely on equipment that is placed with the subject, primarily for monitoring but occasionally for intervention. Finally, there are laboratory or manufacturer-built MRI coils and equipment that need to be properly evaluated.

Regulatory Overview:

In addition to complying with the HHS regulations for the protection of human subjects in research (45 CFR 46) and the Common Rule (45 CFR 46 Subpart A), compliance with the FDA's regulations regarding clinical investigations of products under its jurisdiction, e.g., devices, is required. Briefly, medical devices must be cleared or approved by the FDA for use in humans. In order to study a device or to use an unapproved device, the device must be exempted from the requirements that would normally apply to devices in commercial distribution. Such exemption is achieved through the Investigational Device Exemption (IDE) regulations. For most of the studies conducted in the In Vivo NMR Center, the IRB will act as a surrogate for the FDA under the IDE regulations and may approve the study without direct involvement of the FDA.

NMR Center Safety Committee. Safety related to devices used in the MRI environment is critical. The use of any device within the MRI must be approved in advance by the NMR Center Safety Committee. For legally marketed devices (FDA cleared or approved), the Safety Committee's expertise can be called upon to review the device's labeling and its approved indications for use as well as any available information on the safety of the device if necessary. Be aware that FDA clearance and the related safety assessment may not be applicable for device use in a magnet with a field strength outside of what is currently legally marketed, e.g., 7T. For unapproved devices, e.g., devices provided by a third party or constructed at the NIH, the NMR Center Safety Committee will review the design and any pre-clinical testing and may require additional testing to assure safety. Committee approval is required prior to submission of the protocol or a related amendment to the IRB. The Committee's evaluation and decision regarding relevant devices should be provided to the IRB as an appendix to the protocol submission. While NMR Center Safety Committee approval is necessary for use of devices within the MRI, it is not sufficient. Under the IDE regulations, the responsibility for approval of a study, including the use of any devices in the conduct of the study, rests solely with the IRB.

IRB Review and Approval Process.

- Devices used in the study should be identified and their regulatory status defined, i.e., are they legally marketed devices (cleared or approved by the FDA for marketing) and, if so, what are the indications for use. Within the NMR Center, MRI systems, coils, pulse sequences, software and monitoring equipment as well as devices used for a patient intervention or stimulation are all FDA regulated devices. Any of these items that are not FDA approved or are being used for an indication that is not covered under its labeled indications for use are considered investigational devices.
- If applicable, the IRB will make a determination as to whether the study is exempt from the regulations.

- If the study is not exempt, then the IRB must determine whether the study is a Significant Risk (SR) or Non-Significant Risk (NSR) study, documenting that determination in the record of its review. The SR/NSR determination is based on the risk of the study, not the device. If the study is NSR, then the IRB may then decide whether to approve the study; Center for Devices and Radiological Health (CDRH)/FDA review would not be required. If the IRB determines that the study is SR, then both IRB approval and an IDE application that is approved or conditionally approved by the CDRH/FDA must be in place before the study may begin.

These determinations, i.e., exempt and SR/NSR, are study specific, meaning they can only be made in the context of a specific protocol.

Additional information is available at the FDA's Device Advice website (<https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance>).

Definitions of Devices. The definition of "devices" and information on classification of devices is at <https://www.fda.gov/medical-devices/classify-your-medical-device/product-medical-device>

Exempted investigations. In very rare cases studies that are potentially subject to the IDE regulations may be exempt. This is addressed in 21 CFR 812.2(c):

(<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=812.2>)

If the PI thinks there is grounds for exempting a study or a device they should speak to the IRB.

Significant and Non-Significant Risk studies. A description of Significant Risk and Non-Significant Risk studies can be found [here](#) or in [FDA guidance](#). For MRI systems, there is specific guidance available on the SR determination, Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices available at <https://www.fda.gov/media/71385/download>. This guidance provides the FDA's thinking on the topic. Generally, the FDA deems magnetic resonance diagnostic devices significant risk when used under any of the operating conditions described in the document. They are not affirming, conversely, that studies where the MRI systems are operating below those conditions are non-significant risk. The SR/NSR determination is based on the entirety of the study.

Definitions:

Significant risk device ([21 CFR 812\(m\)](#))

Significant risk 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 a 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 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.

Non-significant risk device study: A study that does not meet the definition for an SR device study.

What the IRB needs to review.

In the protocol, the PI must describe all devices being used in the study. This includes the MRI system, coils, pulse sequences, monitoring equipment, and analysis software. The NMR Center Safety Committee's approval of the use of the devices is required; their review should be provided with the protocol. For devices that are legally marketed (cleared or approved by the FDA for commercial distribution), it is very helpful to the IRB for you to provide the PMA approval or 510K clearance number or approval letter in the IRB application. These are available on the FDA website. This will facilitate the IRB review of the protocol.

The sponsor (or sponsor-investigator) must provide an initial determination as to whether the study is exempt, if applicable, and if not exempt, a determination as to whether the study is SR or NSR. Justification for each determination should be provided, including information regarding safety. As a general comment, unapproved devices, e.g., those fabricated at NIH, may require a more extensive description and discussion of device design and pre-clinical testing prior to use in human subjects.

The IRB will review the protocol, the sponsor's (or sponsor investigator's) risk determination, and for legally marketed devices, the approved intended use statement on the PMA or 510k clearance letter. It is critical to assess each device and/or mode of operation being used in the protocol to make sure its regulatory status is clearly defined. The IRB will review all of the materials in the context of the proposed study and determine whether the study is exempt. If it is not exempt, the IRB must make a formal SR/NSR determination and document its decision:

- **If the IRB determines that the study is NSR**, then the IRB acts on behalf of the FDA and may then decide whether to approve the study under the abbreviated IDE requirements ([21 CFR 812.2.b](#)).
- **If the IRB determines that the study is SR**, then an IDE application must be submitted to the CDRH/FDA. Once the IDE is approved or conditionally approved, the NIH IRB will then decide whether to approve the study. Both approvals must be in place before the study may begin.
- If there is disagreement or uncertainty as to the proper determination, a formal risk determination by the FDA may be requested. The FDA determination is final.

If the IRB or IRBO determines that an FDA determination is required, it will not process the application until the FDA determination has been provided.

Abbreviated IDE Requirements for NSR Studies ([21 CFR 812.2.b](#))

Requirements associated with NSR studies for both Sponsors and Investigators, as well as those for SR studies, can be found at <https://www.fda.gov/medical-devices/device-advice-investigational-device-exemption-ide/ide-responsibilities#resofspoof>. The requirements for NSR studies include, but are not limited to:

- Investigational devices must be labeled, including the statement "CAUTION Investigational device. Limited by Federal (or United States) law to investigational use."
- Additional reporting requirements for both the sponsor (IC) and investigators, which are listed on the website.
- Tracking each use of devices in the research participant's record
- Establishing a monitoring plan. Reporting of adverse device effects is described in the website.

General Comments on Devices Commonly Used in In Vivo NMR Center

Notes related to all devices:

All regulatory issues should be explicitly addressed in the regulatory section of the protocol. Decisions about what to cover in the consent will be study specific.

In several of the sections below, it is noted that use of a type of device is unlikely to cause a study to be determined to be SR requiring CDRH/FDA approval of an IDE. Bear in mind that it is the risk of the entire study that determines SR vs NSR.

MRI Scanners:

Almost all MRI scanners at NIH are FDA cleared and so can be used either for research or clinical purposes. If the system, coils and pulse sequences that are being used in the study are all FDA cleared and are used in accordance with the labeling, then the study may be exempt from the IDE regulations.

Presently there are two MRI scanners that are not FDA approved: the NIMH/NINDS 7T and the NHLBI 0.55T MRI. Any use of these devices is subject to the IDE regulations, but the studies may be NSR. Determining the risk of a study related to the use of any MRI scanner should include evaluation of each of the criteria in the guidance document, Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices, available at <https://www.fda.gov/media/71385/download>. The protocol should provide sufficient information to support the SR/NSR determination. This should include information that the MRI will be operating within FDA safety guidelines to guarantee the safety of the subjects, if that is the case. If the IRB determines the study is NSR, it may then decide to approve the study under the abbreviated IDE requirements.

Peripheral Monitoring Equipment:

- 1) **Devices that are approved or cleared by the FDA for use in the MRI system to be used in the study**, e.g. monitoring devices such as EKG. If the device you are using has been approved for the indicated use, document this in the protocol and provide the PMA approval or 510K clearance letter as an attachment to the IRB application. Be aware that FDA clearance and the related safety assessment may not be applicable for device use in a magnet with a field strength outside of what is currently legally marketed, e.g., 7T.
- 2) **Unapproved devices.** This may include monitoring equipment such as respiratory, cardiac, or EEG that will be used to acquire, improve, or interpret MRI images; peripheral equipment used to affect the function of the participant, e.g., inducing pain, electrical stimulation, etc. As above, information regarding the device including a device description, preclinical evaluation and especially any information related to safety must be included in the protocol. Investigators are required to describe what steps have been taken to make sure the devices are safe in the MRI environment and provisions to ensure safe operation of the equipment during the study. The protocol should provide sufficient information to support the SR/NSR determination for the entire study. In most protocols, it is unlikely that use of these devices will lead to a SR determination.
- 3) **Unregulated devices.** A few devices used in MRI experiments are not regulated by the FDA. For example, these may include response boxes and video cameras. If a device does not meet the FDA's definition of a device, then the protocol should address that determination and may include supporting evidence such as a letter from the manufacturer. Information about safety of the device in the MRI environment will be needed, including approval for use by the NMR Center Safety Committee.

MRI Pulse Sequences: MRI pulse sequences are devices. As above, there is FDA guidance available defining what the FDA considers to be a SR study. The general categories of pulse sequences are:

- 1) **FDA cleared pulse sequences** that are part of the FDA-cleared MRI system as provided by the manufacturer. If the legally marketed device is used in accordance with its labeling, then its use is exempt from the IDE regulations. For example, this would include changing the acquisition

parameters (e.g., TR, TE) for a pulse sequence included on the marketed clinical device within the permitted range. Such use should be stated in the protocol in the section addressing potential regulatory issues.

- 2) **Research pulse sequences with the MRI system operating below each of the SR limits in the FDA guidance.** These would likely be investigational devices and must be evaluated as described above. A key consideration is whether any of the operating conditions exceed those described in the guidance document for SR studies, Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices. If not operating under any of the conditions that the FDA deems to be significant risk, then the study may be determined to be NSR. The justification for the NSR determination should be included in the protocol. The consent is study-specific but might state that research pulse sequences will be used within all the stated FDA safety parameters and that they meet all relevant guidelines for safety. A note should be made in the participant's record that research pulse sequences were used. If an adverse event occurs while running a research pulse sequence this should be reported as part of the adverse event reporting.
- 3) **Studies operating under any of the conditions deemed to be SR in the FDA guidance.** If a study uses pulse sequences where the MRI is operated under any of the conditions deemed to be SR in the FDA guidance, the study likely will be determined to be a Significant Risk study. If the IRB makes that determination, then an IDE application must be submitted to the CDRH/FDA. Once the IDE is approved or conditionally approved, the NIH IRB will then decide whether to approve the study. Both approvals must in place before the study may begin.

Image Reconstruction and Analysis Software: Software that performs image reconstruction and data analysis is an FDA regulated device. The general categories are:

- 1) **FDA cleared software that is considered part of the FDA-cleared MRI system as provided by the manufacturer.** If the legally marketed device is used in accordance with its labeling, then its use is exempt from the IDE regulations. Such use should be stated in the protocol in the section addressing potential regulatory issues.
- 2) **Unapproved research MRI reconstruction and analysis software.** Information regarding the software should be included in the protocol. The Investigator should provide a justification for SR/NSR determination by the IRB. This should include discussion of how the data will be used, e.g., how the software will or might influence the care of the patient. In most protocols, it is unlikely that the use of such software will lead to an SR determination. The consent is study-specific but might state that investigational software will be used.

MRI Coils: Commercially available coils as well as unapproved MRI coils designed and constructed at the NIH or by a manufacturer or other third party are FDA regulated devices. The general categories are:

- 1) **FDA-cleared coils.** If the legally marketed device is used in accordance with its labeling, then its use is exempt from the IDE regulations. Such use should be stated in the protocol in the section addressing potential regulatory issues
- 2) **MRI coils that are not FDA cleared.** Information regarding the coil should be included in the protocol including a device description, preclinical evaluation and especially any information related to safety. The protocol should provide sufficient information to support the SR/NSR determination for the entire study. It is unlikely that use of these devices would lead to a SR determination, again, depending on whether and how the use influences patient care