# FDA Investigational Device Exemptions (IDE): Overview and Application to Research Involving MRI

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**Bethesda, MD**

# Goals

- Cover the concepts of the IDE regulations
- Arm you to
  - Recognize when your study involves investigation of a device
  - Analyze device use in your study
  - Reach correct conclusions on regulatory requirements
  - Present device use and regulatory issues in your protocol, if needed

Distinction between

- IDE regulations: the rules
- IDE or IDE application to the FDA

# IDE Decision Tree

IDE regulatory questions, in order, to reach the correct decisions:

- Is it a device?
- Is it legally marketed/in commercial distribution?
  - If so, what are the indications for use?

- Applicability of IDE regulations to your study
- Is the study exempt?
- If not exempt and is subject to the IDE regulations, is the study (not the device) SR or NSR?

# Outline

- Devices, defined
- Legally marketed; indications for use
- Practice of medicine
- Unapproved/uncleared devices
- IDE regulations and their application
  - Application of the regulations
  - Exemption
  - Significant Risk (SR) vs Non-Significant Risk (NSR) studies
  - Protocol development
  - Approval process for clinical research
- Interacting with the FDA/Guidance
- Examples
- Resources

# Device…

"means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar article, including any component, part, or accessory, which is

1) recognized in the official National Formulary, or the United States Pharmacopeia, 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 which is not dependent upon being metabolized for the achievement of its primary intended purposes"

# Devices

- "Device" refers to
  - the physical device, and
  - its indication for use
- Example: Biliary stents
  - Indication for use: treatment of biliary strictures
  - Use for peripheral arterial disease represents a new device (same physical item, new indication for use)

# Marketing Approval/Clearance

- FDA ensures devices are safe and effective before marketing
- Routes to market
  - Premarket Approval (PMA) (Class III)
  - Premarket Notifications 510(k) (Class II, I)
  - De Novo
  - Humanitarian Device Exemption (HDE)
- **But, route to market is irrelevant to applicability of the IDE regulations**

- What does matter?
  - Is it cleared/approved for marketing for any indication?
  - What is the indication for use, including the purpose and, potentially, the target population? Does it match your proposed use?

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# Practice of Medicine

- FDA is prohibited by law from regulating practice of medicine
- Use of a **legally marketed device** for “off-label” indication as part of practice of medicine for an individual patient
  - Approved IDE not required
  - May require local IRB approval
- Clinical investigation (even one patient) must be conducted in accordance with the IDE regulation

FDA Guidance: "Off-Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices: Guidance for Institutional Review Boards and Clinical Investigators

# Unapproved/Uncleared Devices

- An unapproved medical device may only be used on human subjects when the device is under clinical investigation and when used by investigators participating in a clinical trial.
- Must comply with all applicable requirements

- Devices have to be legally marketed for use in humans (emergency exceptions)
- Cannot simply make a new device and use it in patients
- Legally marketed device that is modified may no longer be the legally marketed device
- It does not matter if the investigation will/will not be used to support a new indication or a significant labeling change by the mfgr. (It can be a factor for INDs)

Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors: Frequently Asked Questions About Medical Devices

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# Investigational Device Exemptions (IDE)

# IDE: Purpose

- Devices have to be legally marketed for use in humans
- Discovery and development of new devices requires exemption from the requirements that apply to devices in commercial distribution
- IDE regulations allow exemption from the normal requirements

21 CFR 812
§ 812.3 Definitions

# IDE: Investigation

- Conduct of a clinical investigation of a medical device requires approval under the IDE regulation
- Investigation: a clinical investigation or research, which involves one or more subjects, to determine the safety or effectiveness of a device
- Sponsor-investigator studies of unapproved devices or new intended use of approved device (even if no marketing application planned) are subject to the regulation

# Decision tree

Questions, in order, to reach the correct answers:

- Is it a device?
- Is it legally marketed/in commercial distribution?
  - If so, what are the indications for use?

- Applicability of IDE regulations to your study
- Is the study exempt?
- If not exempt and is subject to the IDE regulations, is the study (not the device) SR or NSR?

# Exemptions

- An investigation is exempt from the IDE regulation if the device is used or investigated in accordance with the indications in the approved labeling
  - Comparative study of two stents approved for treatment of coronary artery stenosis
  - Study of an approved coronary stent for treatment of intracranial arterial stenosis in the setting of acute stroke
- Indications for Use (IFU):
  - Device Labeling
  - Approval letter: search accessdata.fda.gov and product name

# Significant Risk (SR)/Non-Significant Risk (NSR) studies

- Significant risk study: one which “presents a potential for serious risk to the health, safety, or welfare of a subject.”
- Risk includes risk of any ancillary procedures
- Degree of risk of STUDY, not the device, determines level of regulatory control

§ 812.3(m) Significant risk device

Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies - https://www.fda.gov/media/75459/download

# Significant Risk (SR)/Non-Significant Risk (NSR) studies

- 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;
  - 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.

§ 812.3(m) Significant risk device

Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies - https://www.fda.gov/media/75459/download

# Research Protocol Development

- If there is no investigational device use in the study
  - Can be silent on device use
  - Or, proactive in addressing potential IRB concerns
- Investigational use, including use of unapproved devices or device use not in accordance with the labeling
  - Identify the specific devices (and use)
  - Present the regulatory status, e.g., approved labeling and indications for use; may include FDA approval letter(s)
  - Prior FDA determination
  - How the devices are being used
  - Risk determination for the study, not the devices, although that can be a component

# Protocol Review/Approval Process

- Sponsor (IC): provides initial assessment of risk
- IRB: responsible for determination of SR/NSR
- Non-Significant Risk study: IRB approval
  - IRB acts as a surrogate for the FDA
  - Abbreviated IDE requirements in § 812.2(b)
- Significant Risk study in the US:
  - Both IRB approval and an approved or conditionally approved IDE application are required before the study may begin
- If FDA determines a study is SR or NSR, decision is binding

- If a study is clearly SR, just start with the FDA

IDE Responsibilities: https://www.fda.gov/medical-devices/investigational-device-exemption-ide/ide-responsibilities#resofinvfornon

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# FDA's Pre-Submission Program (Q-sub)

- Informal, confidential feedback
- Generally 60-75 day review
- Letter, phone, email, meeting
- Not required; provides an opportunity for informal FDA feedback to help guide device development
  - Pre-clinical
  - Clinical
- Improves likelihood of IDE approval on 1st or 2nd review cycle

Guidance: Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program (Jan 6, 2021)
https://www.fda.gov/media/114034/download

# Required Elements of an IDE (partial list)

- US sponsor (manufacturer or investigator)
- Description of the device
- Report of prior investigations
- Investigational plan
- Manufacturing information
- Investigator and IRB information
- Sales information
- Labeling
- Informed consent

21 CFR 812
Sec. 812.20 Application

# Guidance

- Guidance: Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices
- Four operating conditions:
  - main static magnetic field
  - specific absorption rate (SAR)
  - gradient fields rate of change
  - sound pressure level
- States operating conditions which the FDA deems SR
- Silent on operation below these conditions, i.e., it is not necessarily NSR

https://www.fda.gov/media/71385/download

# Example 1: Routine Imaging

- Oncologic drug study where RECIST criteria are evaluated using 3T MR to follow tumor progression. All device use is on-label (no research pulse sequences or unapproved coils)
  - Device? Yes
  - Legally marketed? Yes
  - Used per labeling? Yes
  - Exempt as the devices are legally marketed and used per labelling
    - Not a study of safety and effectiveness of device/not object of the study
    - Do not then discuss SR/NSR determination; it is irrelevant. IRB risk/benefit analysis is a separate matter
    - Do not address issues in Definitions, § 812.3(m) Significant risk device
  - Options
    - Be silent in the protocol
    - Or, proactively state, “The MR system, including pulse sequences and coils, is used in accordance with the labeling.”

# Example 2: Research Imaging

- Imaging study using a marketed 3T MR but with research sequences
  - Device? Yes
  - Legally marketed? Yes, but not the research sequences
  - Used per labeling? No. IDE regulations apply
  - Risk determination: SR/NSR
    - Operating below the levels that FDA deems SR? (certainly yes)
    - Assess risk of the study considering use of the devices (imaging only, likely NSR)
  - Discussion in protocol
    - Identify investigational devices. May note relevant components used on-label
    - For MR, note “Use of the MR with research sequences will not exceed any of the limits deemed to represent Significant Risk by the FDA as defined in the guidance document, Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices.”
    - Assessment of risk for the study (SR/NSR), not per device if >1

# Example 2: Research Imaging

- The use of 3T MRI and research pulse sequences in this study do not meet the FDA criteria for a Significant Risk investigations of MR devices and the study may be determined to be Non-Significant Risk. Under 21 CFR 812.3(m), a 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;

    *Response*
  - 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;

    *Response*
  - 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

    *Response*
  - Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

    *Response*

# Example 3: Repetitive Transcranial Magnetic Stimulation (rTMS)

- Use of rTMS to treat a specific neurologic disorder other than depression using the Magstim Rapid2 Therapy System with 3T MR research sequences
  - Devices? Yes
  - Legally marketed? MR: yes, but not sequences; Magstim: yes (K143531)
  - Used per labeling?
    - MR-yes and no, Example 2
    - Magstim Rapid2 Therapy System, K143531
      - Indications for Use: The Rapid2 Therapy System is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode.
  - SR/NSR considerations
    - MR imaging: operating below the levels that FDA deems SR? (certainly yes)
    - Magstim: study operating parameters compared to approved labeling and IFU
    - May consider FDA's, Class II Special Controls Guidance Document: rTMS Systems: Table 2: Maximum Safe Train Duration (seconds) Limits for Avoiding Seizure
  - Protocol: devices, regulatory status/approvals, study use, risk assessment

https://www.accessdata.fda.gov/cdrh_docs/pdf17/K171051.pdf
https://www.fda.gov/media/81495/download

# Resources

- OHSRP Education Series
  - Bench to Bedside to Market: FDA Regulation of Medical Devices, November 4, 2019, William Pritchard and Jonathan Green
  - Investigational Devices: What you need to know and Sponsor and Investigator Responsibilities, April 7, 2022, Jonathan Green and Lisa Goldfeder
- IRBO website
- IC protocol management teams
- CDRH/FDA website
  - Device Advice
  - Guidance documents
  - Online training, education, webinars

https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance

# Learn More

irp.nih.gov

@IRPatNIH

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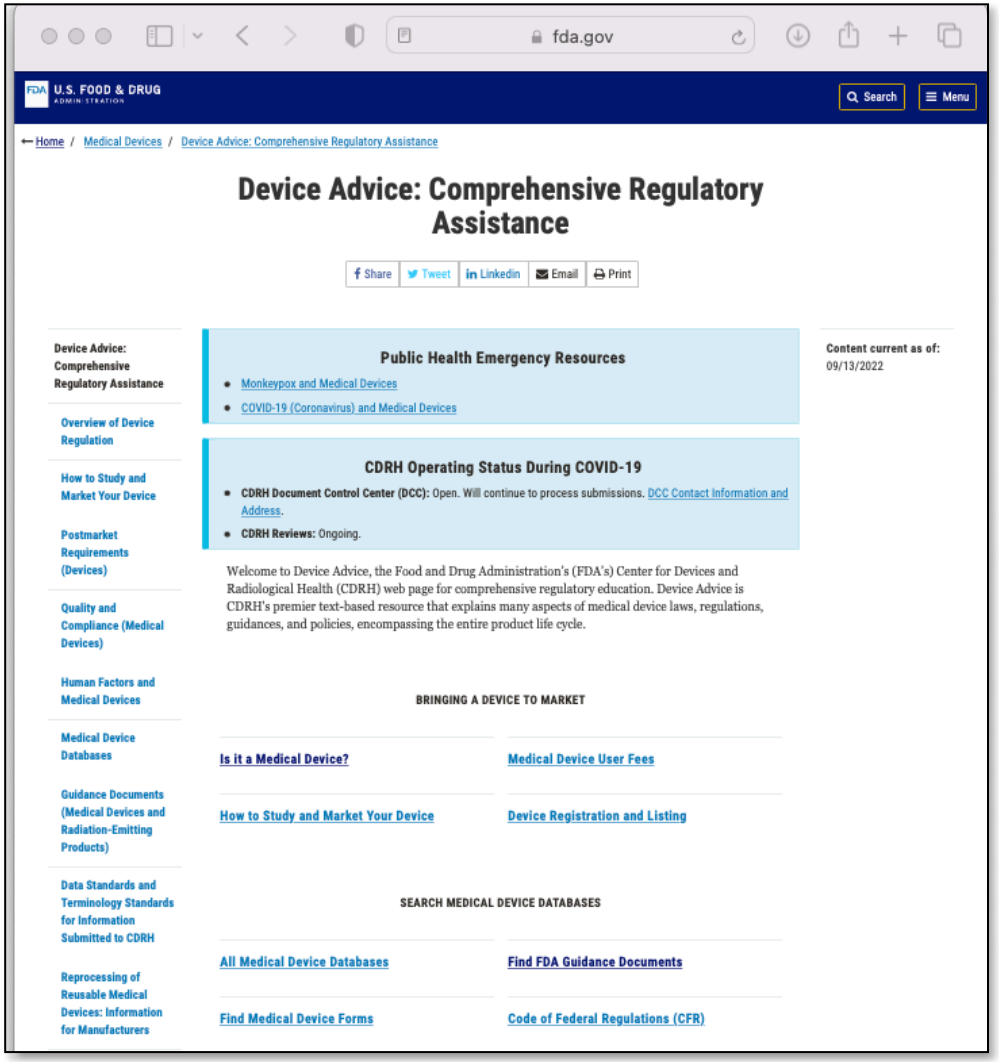
IRPNIH

https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance



# In vivo NMR Center at NIH

**Started in late 1980's as a trans-NIH facility for development and application of MRI with main goal of discovering ways to measure function.**

Institute research programs and a facility for all of NIH.

**Very successful:**

Led in development of high field MRI and related hardware

1.5T to 3T/4T to 7T and now to 11.7T and down to 0.5T.

Led in development of contrast to get tissue function.

fMRI, diffusion/perfusion MRI, variety of new contrast mechanisms.

Many of the users have made important discoveries.

2 human MRIs have grown to 11 MRIs plus associated MRIs nearby.

**Presently ~135 Active Protocols from ~40 PIs and ~250 people log on to MRIs**

Very little clinical MRI for diagnosis.

Some clinical trials that use MRI as biomarker.

Majority of work is research where MRI is a major component.

# MRI in the NMR Center

# In vivo NMR Center at NIH

**How to keep it safe??**

**NMR Center Steering Committee makes all policy in close cooperation with Clinical Center and IRB.**

**Two critical sub-committees:**

**MRI Safety Committee with MRI experts.**

**Clinical Care Committee with clinical experts.**

**Two recent policies:**

**1) More and more people coming with implants. New implant policy.**

**2) With IRB (Bill, Nicole, Jonathan) get device classification up to date.**

**https://intranet2.nmrf.nih.gov/human-imaging**

# Devices in the NMR Center

**Due to research nature of the work, the devices used in the NMR Center have covered the whole range of classification:**

**FDA approved, abbreviated IDE, IDE, and not regulated.**
**The classification is protocol specific but the vast majority of protocols for MRI are NSR using FDA approved, abbreviated IDE, or unregulated devices.**

**Types of devices used in the NMR Center:**

**The MRI system itself**
**MRI detectors/transmitters: RF Coils**
**MRI pulse sequences**
**MRI processing software**
**Peripheral devices that go into MRI with patient.**

# Regulatory Status of NMR Center MRI Systems

## FDA Approve:

NIMH
FMRIF 3T-A GE MR-750
FMRIF 3T-B GE MR-750
FMRIF 3T-D Siemens Skyra
FMRIF 7T-B Siemens Terra

NHLBI
0.55T Siemens Free.Max

NMRF
NMRF 7T Siemens Terra

NIAAA
NIAAA 3T Siemens Prisma

NINDS
Mobile 0.06T Hyperfine

Clinical Center
LDDR 3T Philips Ingenia

## Abbreviated IDE (NSR):

NIMH
FMRIF 7T-A Siemens

NHLBI
NHLBI 0.55T Siemens Aera

## IDE Pending (SR?):

NINDS
NINDS 11.7T Siemens

@NIH Institute, Clinical Dir becomes “the Sponsor”

# NMR Center RF Coils

- **FDA-Approved MRI Coils:**
  If the legally marketed device is used in accordance with its labeling then **Most RF Coils in the NMR Center are FDA Approved**.
  Most commercially available coils fit in this category

- **MRI coils that are not FDA-Approved:**
  **Presently all used under abbreviated IDE:**
  Information regarding the coil should be added to the protocol, including a device description and the preclinical safety evaluation from the NMR Center Safety Subcommittee. Need to provide sufficient detail to support the NSR determination for the entire study.
  Most MRI coils designed and constructed at the NIH fit here but some from third parties and some from MRI vendor are not FDA approved as well.

**If SR then IDE from FDA required: There are presently none like this!**

11.7T IDE will cover Rf coils.

# Examples of Abbreviated-IDE Coils

- Head MRI Coil- 7.0T Volume Transmit Coil, built in-house.
- Head MRI Coil- 0.55T Head Receive Array, built by Siemens.
- Pituitary Coil, built in-house (inquiry to FDA about classification)
- Siemens 7T Terra Parallel Transmit MR System, which includes an 8Tx/32Rx-7T Head Coil built by Nova Medical; tested and supplied by Siemens.

# MRI pulse sequences are devices

1. **FDA cleared pulse sequences:**

   They are part of the FDA-cleared MRI system as provided by the manufacturer. Clinical decisions can be made.

2. **Research pulse sequences:**

   If FDA limits are followed for RF heating (SAR) and Time-varying magnetic field gradients (dB/dt), then the study may be determined to be Not Significant Risk (NSR). The justification for the NSR determination should be included in the protocol. The pulse sequence is used under an **abbreviated IDE**. Since all of these sequences are within FDA limits specific sequences do not have to be listed.

If FDA limits are exceeded for RF heating (SAR) and Time-varying magnetic field gradients (dB/dt), then the study may be determined to be a Significant Risk (SR). The NMR Center Safety Committee should know and comment on these. There are presently **NO** examples of this but an IDE may be required.

**If research goal of protocol is to show clinical efficacy then IRB approval and an IDE application may be required.**

# Image Reconstruction and Analysis Software are devices

1. **FDA cleared MRI reconstruction and analysis software**

- They 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. Such use should be stated in the protocol in the section addressing potential regulatory issues.

  Can be used for clinical purposes

2. **Research MRI reconstruction and analysis software**

- Could be built-in-house, third party, and are not FDA approved.

  A statement that research software will be used should be included in the protocol along with a justification for SR/NSR determination by the IRB.

  This should include discussion of how the data will be used, ad that the software will not be used to might influence the care of the patient.

  Needs IRB and maybe FDA IDE clearance to be used for research that my use software for clinical decisions.

# MRI Peripheral Devices

1. Devices carrying an FDA 510(k) clearance (equivalent to FDA approved).
   - The Sponsor needs to determine if the device is used in the trial in accordance with this label.
     - OptoActive Noise control and communication system (OptoAcoustics)

2. Devices that meet the criteria for FDA exemption (not regulated).
   - The Sponsor needs to determine if the device meets the criteria for 'Exemption' under 812.2(c)(3) and is not subject to regulatory action under 21CFR812.
     - MRI compatible video camera (MRC Systems), button boxes for responses.
     - Physiological monitoring system (BIOPAC System, Inc)
     - NIBP-A-MRI CareTaker4 Blood pressure system (BIOPAC System, Inc)
     - Motion correction camera (KinetiCor)
     - Response monitoring button box (Current Designs, Inc)

     **These devices should be reported on protocol and need approval to enter the MRI by the NIH NMR Safety Committee.**

# Other Abbreviated IDE Devices

- BrainAmp MR plus EEG device (Brain Products, GmbH):
  - There is no market clearance or approval for this device in the US and the device does not meet criteria for exemption under 21CFR812.
  - This device has not received pre-market approval or 510 (K) clearance by the FDA.
  - The intended use of this device in the study, the study population, and the device not meeting the criteria for a Significant Risk Device Study under 21CFR 812.3(m), the Sponsor's determination is that the device used in this study poses non-significant risk (NSR) to human subjects.

**All abbreviated IDE Devices should be approved by the NMR Center Steering Committee.**

# FDA Investigational Device Exemptions (IDE): The NINDS Approach

Lauren Reoma, MD, FAAN
Director, NINDS Clinical Trials Unit

CLINICAL TRIALS UNIT

NIH National Institute of Neurological Disorders and Stroke

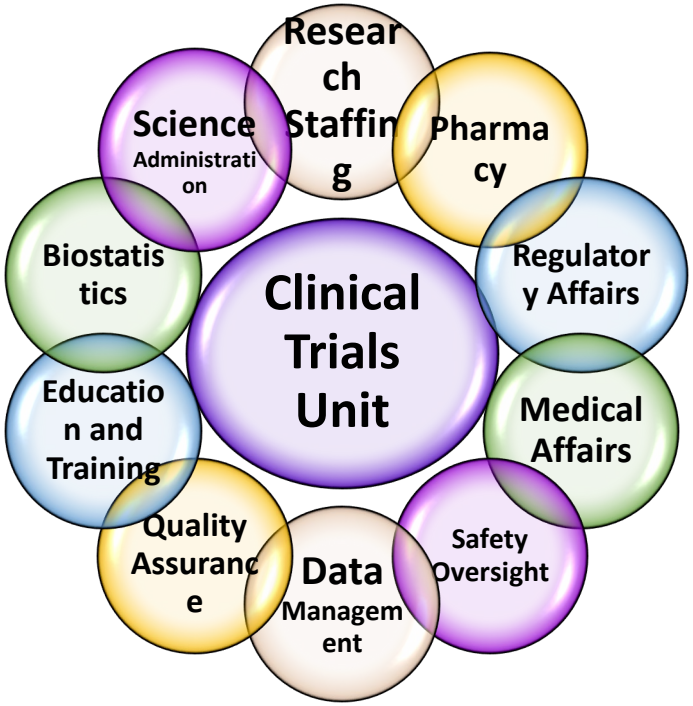
# Objectives

- Describe the NINDS IDE review process and support structure
- Recognize key expedited NSR reporting considerations for clinical teams

# Centralized Clinical Research Support

NINDS Clinical Trial Unit Supports:

- 3 NIH ICs
- 126 active clinical protocols
- 27 clinical faculty
- 31 non-clinical faculty



# Protocol Development Meeting

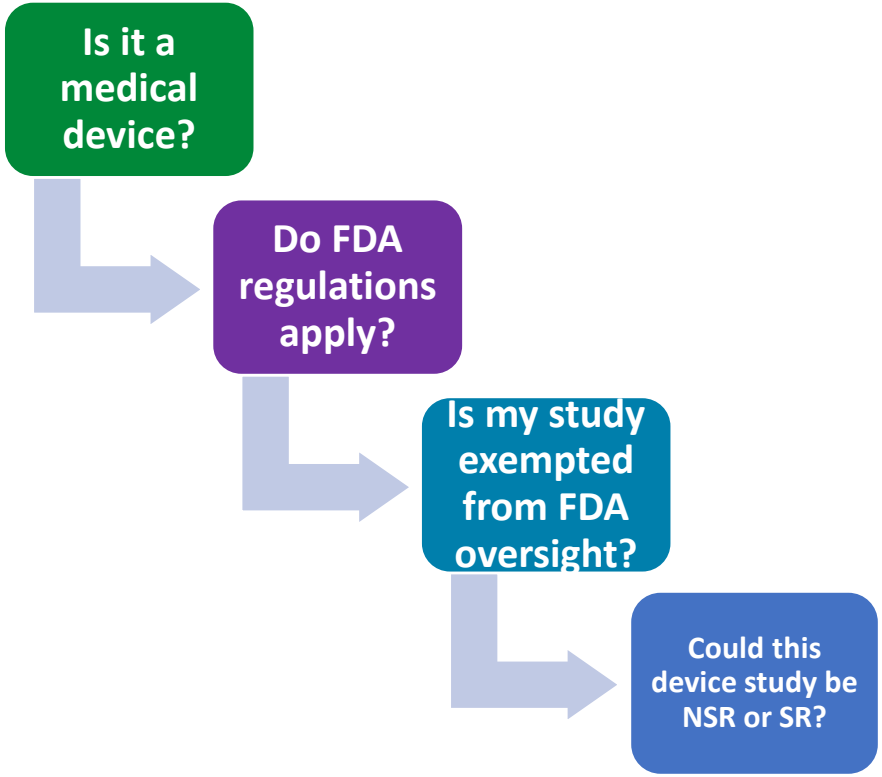

**Required for:**

- Investigational New Drug [IND] or Investigational Device Exemption [IDE] studies
- Multi-center clinical trials
- Clinical Trials involving external sponsors
- Clinical Trials involving a Fellow as PI or LAI

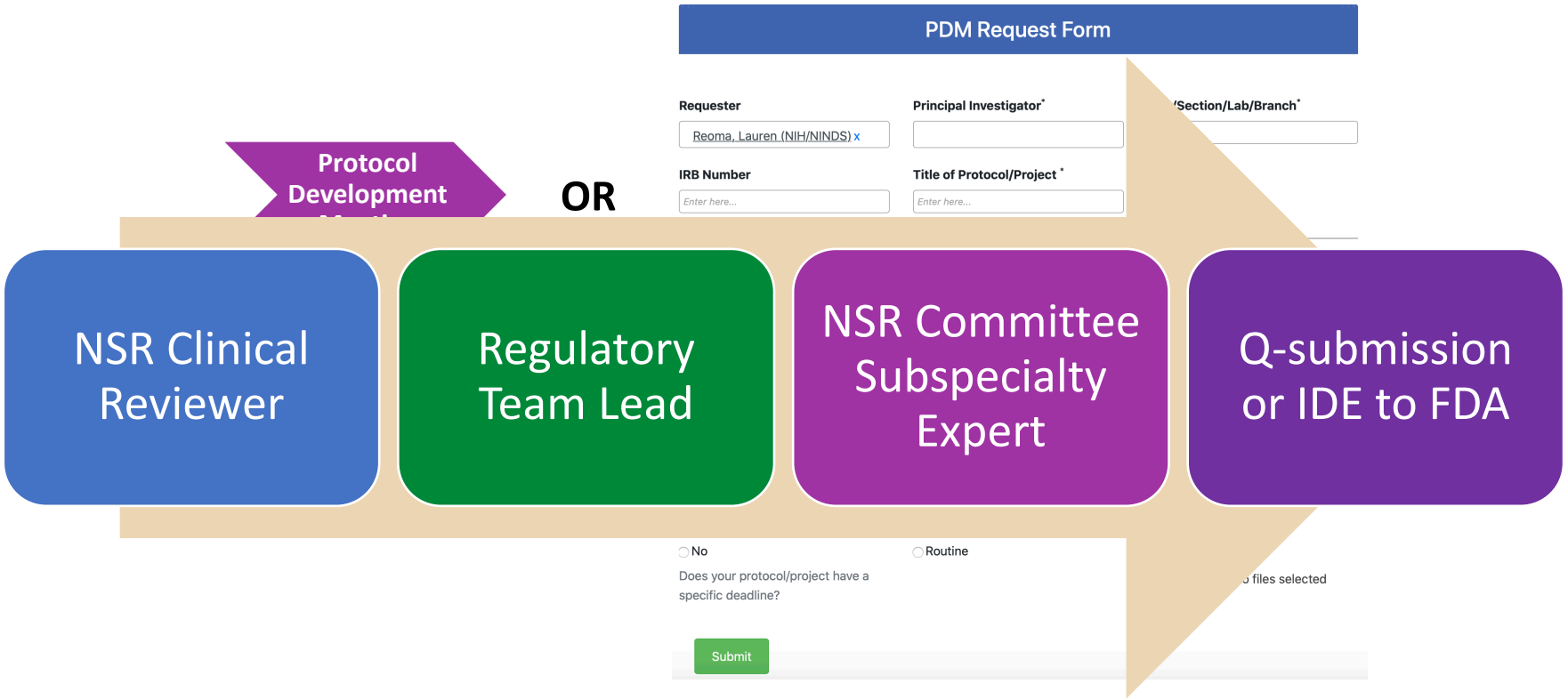
**Purpose:**

- Reduce stipulations at Scientific Review and IRB
- Identify critical aspects of protocols
- Ensure compliance with the regulations

# Protocol Review



# NSR Determination



# Sample Protocol Language

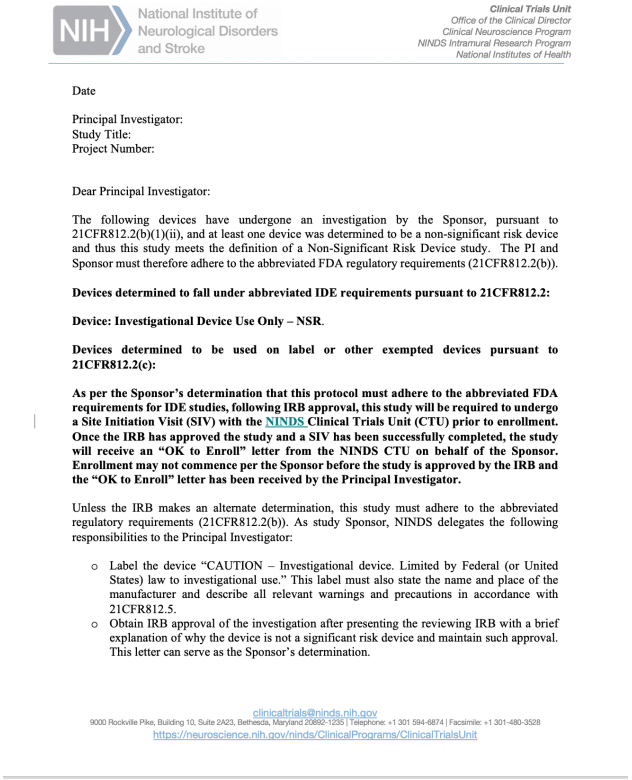
The X device is not FDA approved; it is being used as XXX in this study. According to 21 CFR 812.3(m), a significant risk device presents a potential for serious risk to the health, safety, and welfare of a subject and meets the significant risk criteria listed in the table below along with the sponsor's conclusions regarding the applicability of these criteria to the current study. The device has been assessed by the sponsor as a non-significant risk per the below.

Contact for NSR Determination XXX:
Name MD, Phone: XX, Email: XX

| Significant Risk Criteria | Applicable | Justification in current study |
|---|---|---|
| **Is an implant** | No | All devices listed in this section are not intended as implants and do not present a potential for serious risk to the health, safety, and welfare of a subject |
| **Is supporting or sustaining human life** | No | All devices listed in this section are not purported or represented to be for a use in supporting or sustaining human life and presents no potential for serious risk to the health, safety, or welfare of a subject. |
| **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** | No | All devices listed in this section are not intended for use of substantial importance in diagnosing, curing mitigating, or treating disease, or otherwise preventing impairment of human health and presents no potential for serious risk to the health, safety, or welfare of a subject. |
| **Otherwise poses a risk** | No | All devices listed in this section do not present a potential for serious risk to the health, safety, or welfare of subjects. |

# Training

- Required on all new NINDS-Sponsored NSR or SR studies
- Provided by the CTU regulatory office

NIH National Institute of Neurological Disorders and Stroke

*Clinical Trials Unit*
*Office of the Clinical Director*
*Clinical Neuroscience Program*
*NINDS Intramural Research Program*
*National Institutes of Health*

Date

Principal Investigator:
Study Title:
Project Number:

Dear Principal Investigator:

The following devices have undergone an investigation by the Sponsor, pursuant to 21CFR812.2(b)(1)(ii), and at least one device was determined to be a non-significant risk device and thus this study meets the definition of a Non-Significant Risk Device study. The PI and Sponsor must therefore adhere to the abbreviated FDA regulatory requirements (21CFR812.2(b)).

**Devices determined to fall under abbreviated IDE requirements pursuant to 21CFR812.2:**

**Device: Investigational Device Use Only – NSR.**

**Devices determined to be used on label or other exempted devices pursuant to 21CFR812.2(c):**

**As per the Sponsor's determination that this protocol must adhere to the abbreviated FDA requirements for IDE studies, following IRB approval, this study will be required to undergo a Site Initiation Visit (SIV) with the NINDS Clinical Trials Unit (CTU) prior to enrollment. Once the IRB has approved the study and a SIV has been successfully completed, the study will receive an "OK to Enroll" letter from the NINDS CTU on behalf of the Sponsor. Enrollment may not commence per the Sponsor before the study is approved by the IRB and the "OK to Enroll" letter has been received by the Principal Investigator.**

Unless the IRB makes an alternate determination, this study must adhere to the abbreviated regulatory requirements (21CFR812.2(b)). As study Sponsor, NINDS delegates the following responsibilities to the Principal Investigator:

- Label the device "CAUTION – Investigational device. Limited by Federal (or United States) law to investigational use." This label must also state the name and place of the manufacturer and describe all relevant warnings and precautions in accordance with 21CFR812.5.
- Obtain IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device and maintain such approval. This letter can serve as the Sponsor's determination.

clinicaltrials@ninds.nih.gov
9000 Rockville Pike, Building 10, Suite 2A23, Bethesda, Maryland 20892-1235 | Telephone: +1 301 594-6874 | Facsimile: +1 301-480-3528
https://neuroscience.nih.gov/ninds/ClinicalPrograms/ClinicalTrialsUnit

# Quality Assurance

- Monthly non-compliance tracking of all NINDS and affiliated IC protocols in CiSTAR
- Protocol monitoring according to NINDS SOP 12: Quality Assurance Auditing

# What are your responsibilities? (21CFR812)

- **Ensuring that an investigation is conducted according to** :
  - The signed investigator agreement,
  - The investigational plan
  - Applicable FDA regulations,
- **Protecting the rights, safety, and welfare of subjects under the investigator's care**
- **Control of devices under investigation.**
- **Ensuring that informed consent is obtained**
- **Awaiting approval from IRB before giving Informed Consent**
- **Compliance**
  With protocol, signed agreement with sponsor, and applicable FDA and IRB regulations
- **Supervising device use**
  Use only with subjects!
- **Financial disclosures to the sponsor (when applicable)**
- **Disposing of device**
  When clinical investigation is over, or investigator's part is over, or at sponsor's request

Slides courtesy of Dana Evans

# Responsibilities - continued (21CFR812)

- **Reporting**
  - Submit unanticipated adverse device effects (21CFR 812.3s) to NINDS CTU
  - Notify NINDS CTU of any device recall, repair, or disposal

- **Records**
  - Document device accountability; i.e. records of shipment and disposition of the device
  - Document adverse device effects (whether anticipated or unanticipated) and complaints
  - Submit final report on the study to IRB and FDA within 6 months of study completion

**Slides courtesy of Dana Evans**

# Expedited regulatory considerations

- Unanticipated adverse device effects - within 10 working days
- Withdrawal of IRB approval - within 5 working days
- Lack of informed consent - within 5 working days after the occurrence
- Among others…

**Slides courtesy of Dana Evans**

# Example 1

- NINDS-SAR@nih.gov

**Expedited Reporting Event**

- MRI device study failed to obtain consent prior to scan
- Subject received and reviewed consent
- Intended study visit canceled, log mislabeled as “consented”
- Participant completed NMR center MRI Safety Screening Questionnaire
- Scanned on two 3T scanners


**Failure to Obtain Informed Consent Review Complete**

[redacted]
Report for protocol, [redacted]

This document is being communicated via e-mail as an attachment. The date on which FDA sent this e-mail is the official date of this correspondence.

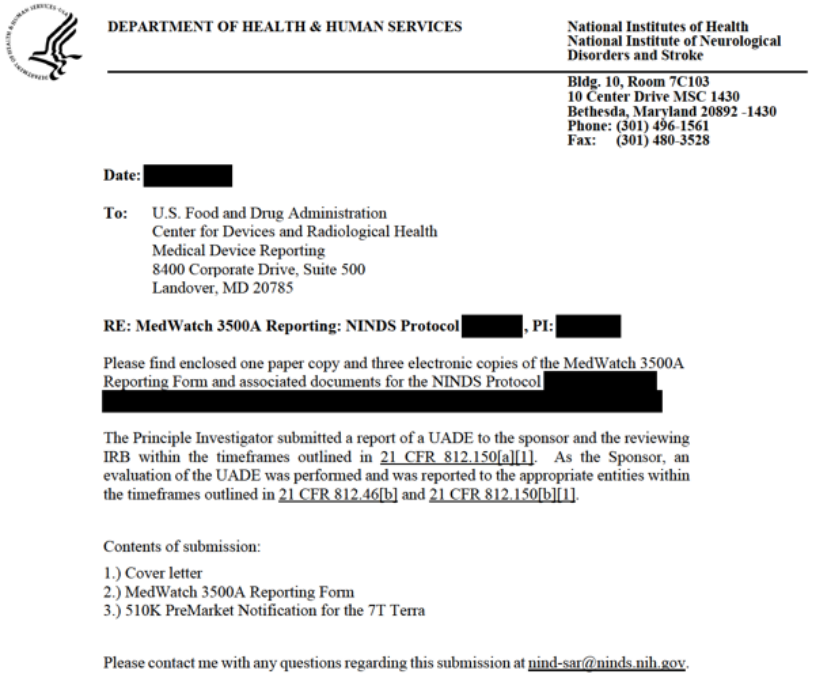
The Food and Drug Administration (FDA) has reviewed the Failure to Obtain Informed Consent in your investigation, in your report dated January 26, 2022, and has determined that you have met the requirements of 21 CFR 812.150(b)(8). No further information is required at this time. This notification is being sent in lieu of a formal written letter.

# Example 2

- NINDS-SAR@nih.gov

**Expedited Reporting Event #2**

- Participant scanned on 7T MRI
- Experienced sustained dizziness for more than 24 hours
- Discovered on follow up phone visit by PI and team
- Clinical care provided to patient and Sponsor alerted
- Determined to meet UADE criteria by both Sponsor and PI
  - unexpected duration and severity of expected dizziness
  - definitely related to NMR exposure



DEPARTMENT OF HEALTH & HUMAN SERVICES

National Institutes of Health
National Institute of Neurological Disorders and Stroke

Bldg. 10, Room 7C103
10 Center Drive MSC 1430
Bethesda, Maryland 20892 -1430
Phone: (301) 496-1561
Fax: (301) 480-3528

**Date:** [redacted]

**To:** U.S. Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
8400 Corporate Drive, Suite 500
Landover, MD 20785

**RE: MedWatch 3500A Reporting: NINDS Protocol** [redacted]**, PI:** [redacted]

Please find enclosed one paper copy and three electronic copies of the MedWatch 3500A Reporting Form and associated documents for the NINDS Protocol [redacted]

The Principle Investigator submitted a report of a UADE to the sponsor and the reviewing IRB within the timeframes outlined in 21 CFR 812.150[a][1]. As the Sponsor, an evaluation of the UADE was performed and was reported to the appropriate entities within the timeframes outlined in 21 CFR 812.46[b] and 21 CFR 812.150[b][1].

Contents of submission:

1.) Cover letter
2.) MedWatch 3500A Reporting Form
3.) 510K PreMarket Notification for the 7T Terra

Please contact me with any questions regarding this submission at nind-sar@ninds.nih.gov.

# Summary

- Centralization for the NINDS intramural clinical neuroscience program
  - Protocol Review and Device Determination
  - Point person for NSR review and initial determination
    - Regulatory team lead review
    - NSR sub-specialty review
    - Q-submission and/or IDE submission
  - Quality Assurance
    - Auditing
    - Compliance monitoring through central database
  - Central email box for questions or adverse event reporting (NINDS-SAR@nih.gov)
    - Monitored daily

# Thank you!

- Please contact the NINDS Clinical Trials Unit with any questions

  Director: Lauren Reoma MD (lauren.reoma@nih.gov)

  Deputy Director: Sandy Martin MS (sandy.martin@nih.gov)

  Regulatory Team Lead: Dana Evans (dana.evans@nih.gov)