Investigational Devices

What you need to know and when you need to know it.

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The plan

IRB side of investigational devices –Jonathan Green

Sponsor/PI responsibilities once the study is approved – Lisa Goldfeder

Investigational device studies

FDA regs and definitions

What is a device?

How are devices approved?

What is an investigational device?

When is an IDE needed?

What is a Significant Risk (SR) or Non-Significant Risk (NSR) device?

What are the IRB responsibilities?

Case examples

Definitions

FDA

56.102(c) ***Clinical investigation*** means any experiment that involves a test article and one or more human subjects……..The terms *research, clinical research, clinical study, study,* and *clinical investigation* are deemed to be synonymous for purposes of this part

56.120(l) ***Test article*** means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act ….

COMMON RULE

Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.

Definitions

FDA

812.3(p) *Subject* means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease.

50.3(g) *Human subject* means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient

COMMON RULE

Human subject means a living individual about whom an investigator (whether professional or student) conducting research:

- (i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
- (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens

Scope

Scope of the Common Rule and FDA regulations differ and that may mean some studies may not be human subjects research under the Common Rule, but still be a clinical investigation of a device and require IRB review under FDA regs.

- Anonymized tissue/data

Review comparison table found here:

https://www.fda.gov/science-research/good-clinical-practice-educational-materials/comparison-fda-and-hhs-human-subject-protection-regulations

https://www.hopkinsmedicine.org/institutional_review_board/guidelines_policies/guidelines/fda_ohrp.html

What is a device?

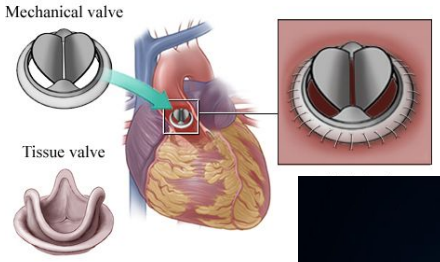
A medical device is an *instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory*, which is—

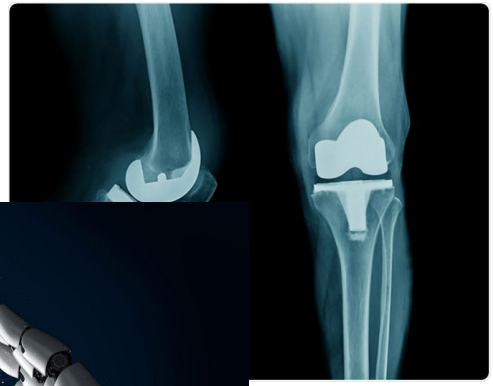
- recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
- *intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or*
- intended to affect the structure or any function of the body of man or other animals, and

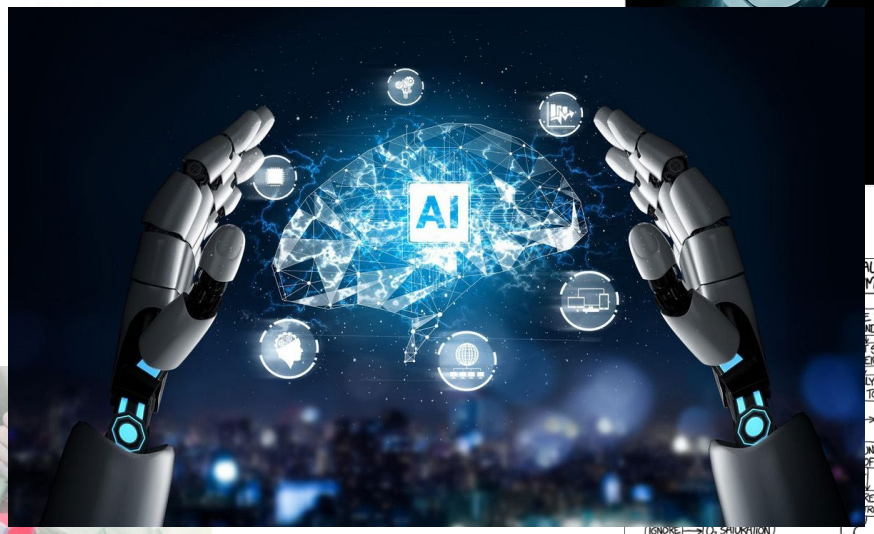
which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes (21 U.S.C. 321(h)).

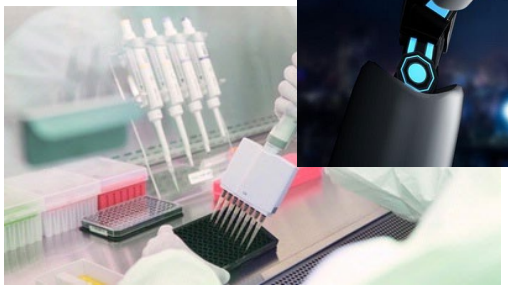
(g) *Investigational device* means a device, including a transitional device, that is the object of an investigation.

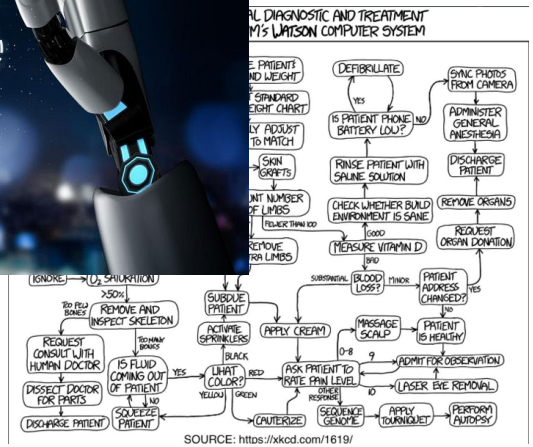
Devices











SOURCE: https://xkcd.com/1619/

What is an IDE?

An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data.

- All clinical evaluations of investigational devices, unless exempt, must have an approved IDE **before** the study is initiated.

An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with other requirements of the Food, Drug, and Cosmetic Act (FD&C Act) that would apply to devices in commercial distribution.

How are devices approved?

Premarket Approval

- Most stringent
- Requires submission of controlled trials demonstrating safety and efficacy
- Assigned a PMA#, which carries over to the approval
- Listed at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

Premarket notification (510k clearance)

- Clearance to market based on an FDA determination that the new device is substantially equivalent to a legally marketed device for which a PMA is not required
- May or may not require clinical study data
- Listed at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm

Exempt

- Subject only to "general controls"
- Most class I and a few class II
- Listed at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/315.cfm

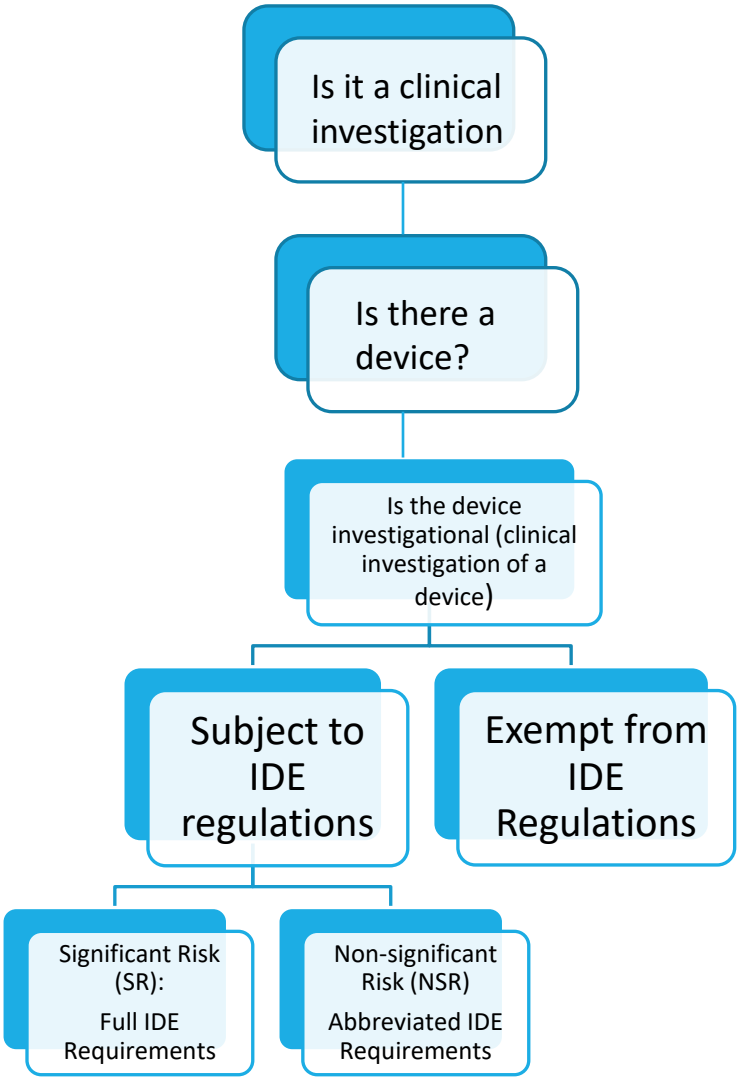
What is an Investigational Device?

Investigation means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device. (21 CFR 812.3(h))

Investigational device means a device, including a transitional device, that is the object of an investigation. (21 CFR 812.3(g))

Subject means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease. (21 CFR 812.3(p))

When do you need an IDE?



When do you NOT need an IDE

Practice of Medicine

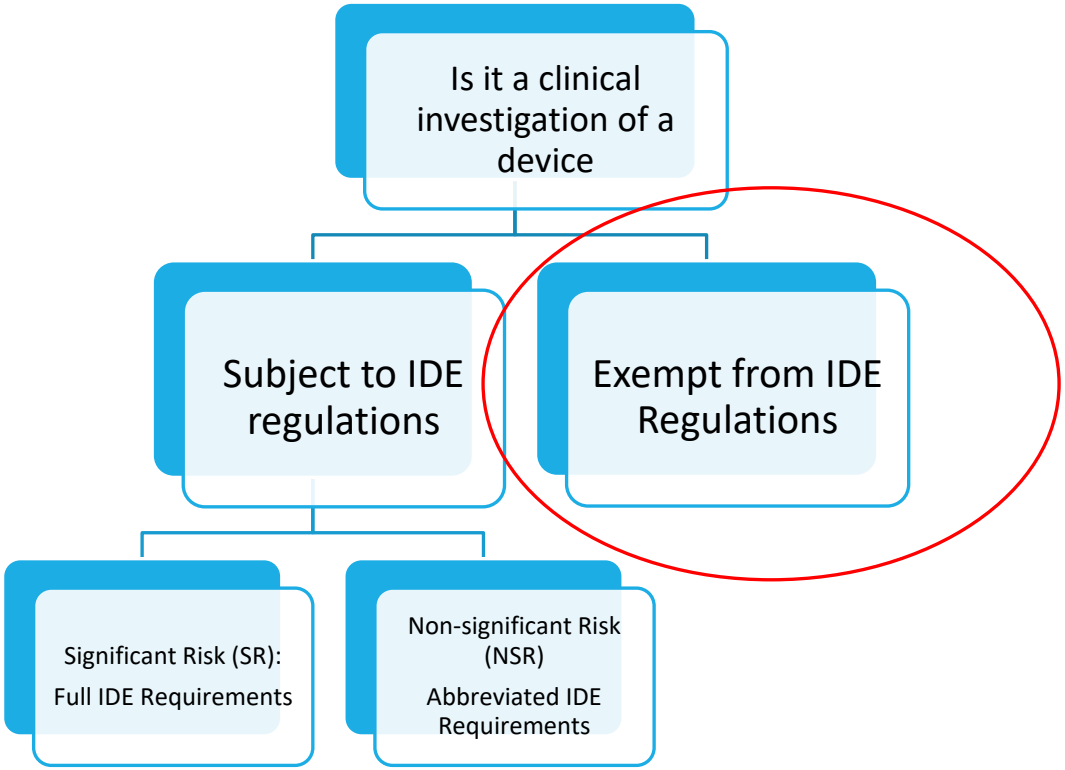
- Off label therapeutic use within the practitioner-patient relationship
- Device must be approved for some use, not necessarily the planned use
  - No “off label” use of unapproved devices

When the device is not the object of the investigation

- “Basic Physiologic Research”

When it is exempt from the requirement for an IDE

When do you need an IDE?



IDE Exempt

(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.

(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.

How do you know the FDA approved use?

Look it up!

- PMA approvals http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm
- 510k approvals: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm
- Exempt: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/315.cfm

Studies of a NEW use of an approved device are NOT exempt (except maybe an IVD)

IDE Exempt

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

- Is noninvasive,
- Does not require an invasive sampling procedure that presents significant risk,
- Does not by design or intention introduce energy into a subject, and
- Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

IDE Exempt

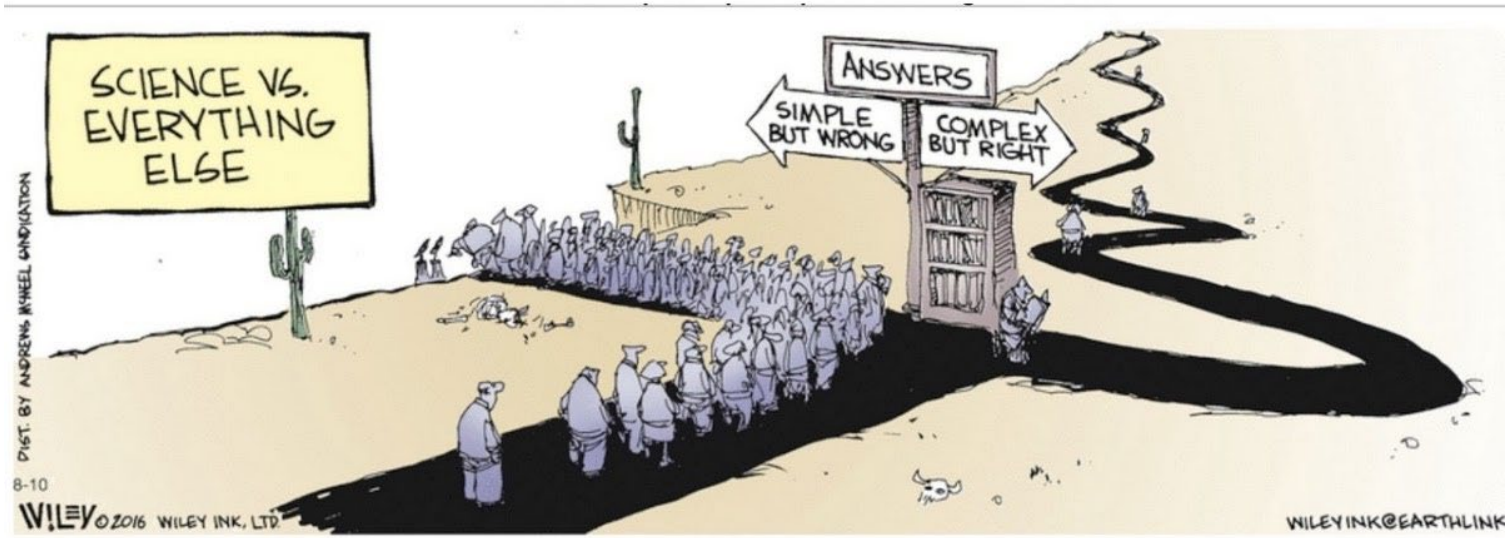
(4) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.

(5) A device intended solely for veterinary use.

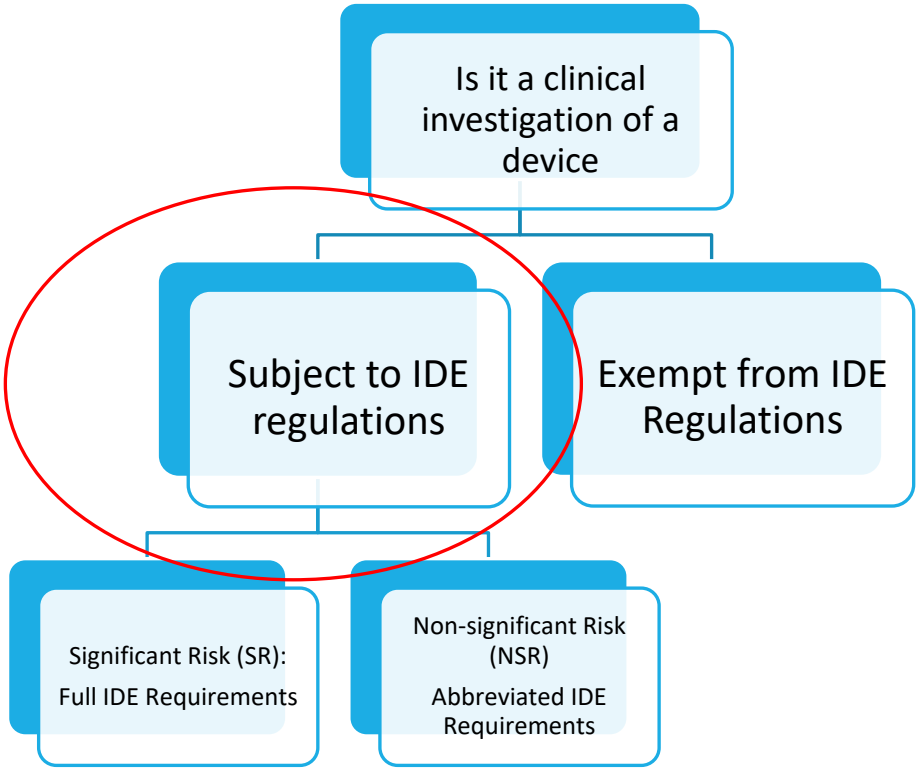
(6) A device shipped solely for research on or with laboratory animals and labeled in accordance with § 812.5(c).

Not IDE exempt

Any other clinical investigation testing the safety and efficacy of a device



When do you need an IDE?



SR or NSR

Significant Risk

- requires application to the FDA and assignment of IDE #, full IDE requirements

Non-significant risk

- abbreviated IDE requirements, IRB review, no application to the FDA
- Only full board can make NSR determination

NOT the same as the FDA class

NOT the same as the minimal risk determination.

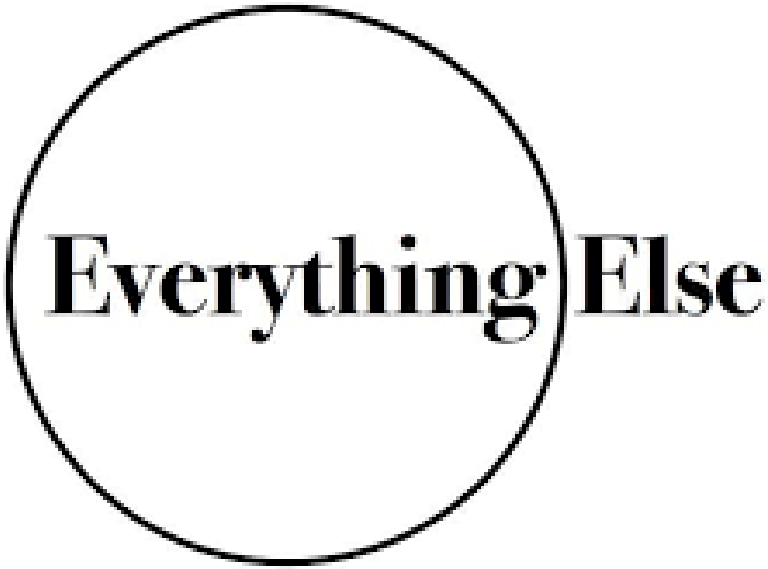
What is Significant Risk?

12 CFR 812.3(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.

What is Non-Significant risk?

An NSR device study is one that does not meet the definition for an SR device study



Who decides SR vs NSR

If previously decided by the FDA, sponsor should provide the determination letter.

If no previous FDA decision, sponsor makes initial determination.

IRB must review and either agree or modify the sponsor determination if they disagree.

FDA is final arbiter if submitted.

Deciding Risk

Review sponsor/PI information.

What is the basis for the risk?

- Proposed use of the device, not the device alone.

What is the nature of the harm that may result?

- Potential for serious risk to health, safety or welfare

Are there any additional procedures with potential for harm?

- Harm of the procedure should be considered, not just the device.

Device determinations are ***study specific***

- It is the risk of the device in the study, not the device alone

What does the IRB need?

Protocol

- Description of the device (manufacturer, model, components etc)
- FDA approved indication for use (if an approved device)
  - If you have the 510k or PMA letter…please provide!
- If claiming IDE exempt or NSR, justification for why this study meets those regulatory requirements
  - Sponsor justification (if sponsored study)
  - Prior FDA determination for this study (or a similar study) if it exists

Consent

- A statement that the device is investigational
- Description of the device, procedure, risks

Example 1

An investigator proposes to study the incidence of stroke in patients that receive the Edwards Sapien transcatheter 9600TFX heart valve. Eligible patients with severe calcific aortic stenosis that are symptomatic from their disease and judged to be too high risk for open surgery will be enrolled. (PMA # P140031)

Questions

- Is it a clinical investigation? YES
- Is there a device YES
- Is it investigational YES
- Exempt
- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm
- NSR/SR

Example 2

An investigator proposes to study the incidence of stroke in patients that receive the Edwards Sapien transcatheter 9600TFX heart valve. Eligible patients with aortic stenosis due to a bicuspid aortic valve that are symptomatic from their disease and judged to be too high risk for open surgery will be enrolled. (PMA # P140031)

Questions

- Is it a clinical investigation? YES
- Is there a device YES
- Is it investigational YES
- ~~Exempt~~
- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm
- NSR/SR

Example 3

An investigator is studying a new treatment for glioblastoma multiforme. The patients will receive the investigational drug, and standard MRI scans using approved sequences and magnets with gadolinium before treatment and after each cycle of therapy to determine the effectiveness of the drug.

Questions

- Is it a clinical investigation? YES
- Is there a device YES
- Is it investigational NO
- Exempt n/a
- NSR/SR n/a

Example 4

An investigator is interested in brain structure and function in individuals with major depression. She wishes to determine if a particular imaging technologies are better then others at identifying changes associated within the brain. She thinks this could be used in the future for diagnostic purposes. She proposes to enroll people diagnosed with depression and perform MRI scans with 2 commercially FDA-approved scanners using standard FDA-approved sequences.

Questions

- Is it a clinical investigation? YES
- Is there a device? YES
- Is it investigational? YES
- Is it exempt? YES
- Is it NSR or SR? n/a

Example 5

An investigator is interested in how brain function may differ between individuals with normal mood and major depression. She proposes to enroll controls and people diagnosed with depression and perform routine fMRI studies as well as use a novel coil developed in her lab to image the brain and see if this new coil can detect changes in brain structure and function that correlate with depression. She hopes this will eventually be a tool that can be used to diagnose and guide treatment for depression.

Questions

- Is it a clinical investigation? YES
- Is there a device? YES
- Is it investigational? YES
- Is it exempt? NO
- Is it NSR or SR? NSR

Resources

501 - Policy - Research Involving FDA Regulated Devices

502 - Policy - Expanded Access, Including Emergency Use of Investigational Drugs, Biologics, and Medical Devices (Test Articles)

501. Guideline for Device Classification for Protocols using MRI in the NMR Center.pdf

Interventional drug or device clinical trial protocol template

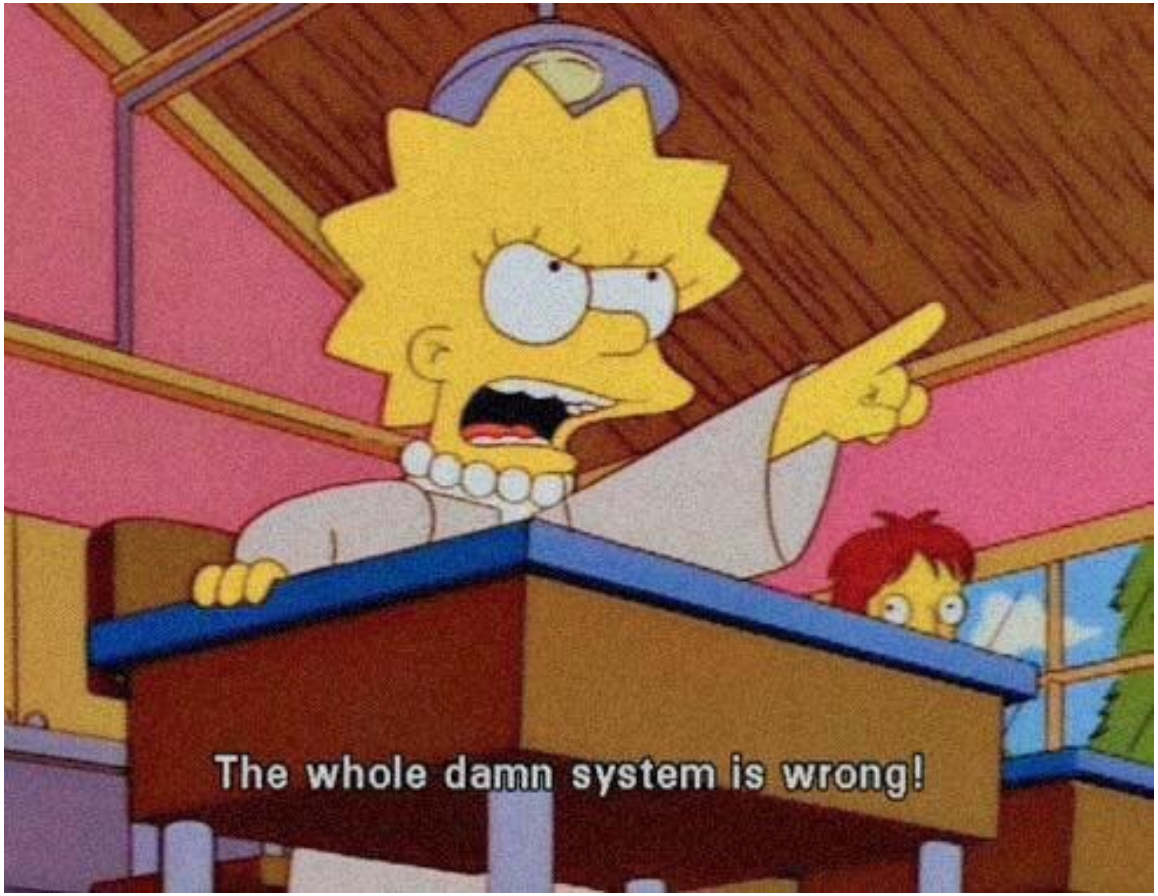
FDA guidance: FDA Decisions for Investigational Device Exemption Clinical Investigations; Guidance for Sponsors, Clinical Investigators, Institutional Review Boards, and Food and Drug Administration Staff

FDA guidance: Significant Risk and Nonsignificant Risk Medical Device Studies - Information Sheet (PDF - 211KB)

https://www.fda.gov/medical-devices/ivd-regulatory-assistance/overview-ivd-regulation

FDA guidance: In Vitro Diagnostic (IVD) Device Studies - Frequently Asked Questions

FDA guidance: Investigational IVDs Used in Clinical Investigations of Therapeutic Products


The whole damn system is wrong!

Sponsor and Investigator Responsibilities: Investigational Device Exemptions (IDEs)

Lisa Goldfeder, CCRP, RAC

April 7, 2022

I Have a Determination for my study…so now What?

Sponsor—IC

- Submits SR IDE applications to the FDA
- Holds the approved IDE application (SR and NSR)

Investigator (Principal Investigator)

- Submits NSR Device Studies to the IRB
- Conducts the clinical investigation

Each have responsibilities under 21 CFR 812

Five FDA Actions on SR IDE

- Approval
  - Study can start with IRB approval
  - No additional conditions

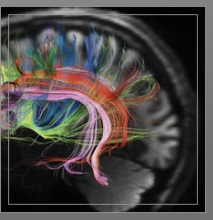
- Approval with Conditions
  - No safety concerns; enrollment can begin
  - Conditions must be addressed within 45 days

Five FDA Actions on SR IDE (Continued)

- Staged Approval
  - Allows enrollment to begin for a portion of the cohort while outstanding questions addressed

- Staged Approval With Conditions
  - Allows enrollment to begin for a portion of the cohort
  - Conditions must be addressed within 45 days

- Disapproval
  - Cannot start until deficiencies are addressed




When Approval Comes: Sponsor Responsibilities

Sponsor Responsibilities-Overview
21 CFR 812 Subpart C

SR Device Studies

FULL IDE requirements under
21 CFR 812

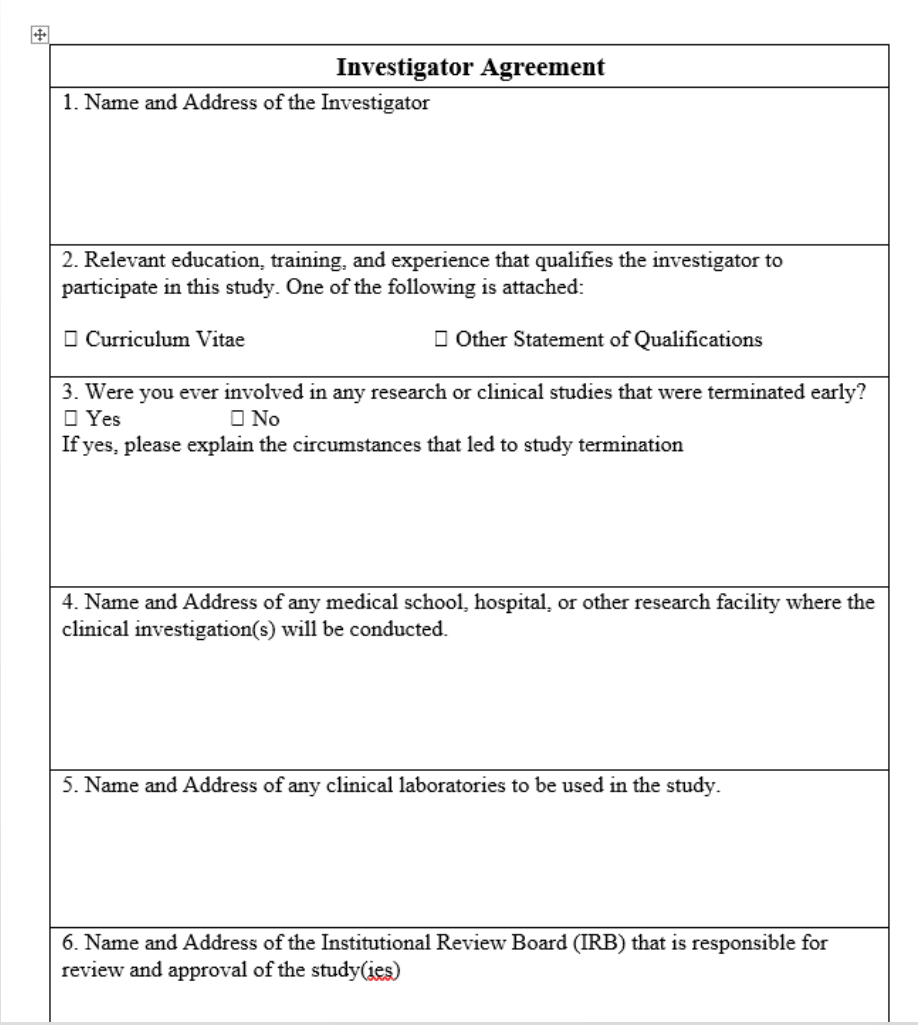
NSR Device Studies

Abbreviated IDE requirements
under 21 CFR 812.2(b)

Labeling
IRB approval
Informed Consent
Monitoring
Records (abbreviated)
Reports (abbreviated)
Prohibition against promotion

Sponsor Responsibilities-Overview
21 CFR 812 Subpart C

- Selecting qualified investigators
- Obtaining Investigator Agreement
- Providing investigators with the information they need to conduct the investigation properly
- Control of the Device (i.e, ship only to qualified investigators)



Investigator Agreement
1. Name and Address of the Investigator
2. Relevant education, training, and experience that qualifies the investigator to participate in this study. One of the following is attached: ☐ Curriculum Vitae ☐ Other Statement of Qualifications
3. Were you ever involved in any research or clinical studies that were terminated early? ☐ Yes ☐ No If yes, please explain the circumstances that led to study termination
4. Name and Address of any medical school, hospital, or other research facility where the clinical investigation(s) will be conducted.
5. Name and Address of any clinical laboratories to be used in the study.
6. Name and Address of the Institutional Review Board (IRB) that is responsible for review and approval of the study(ies)

Sponsor Responsibilities-Overview
Labeling 21 CFR 812.5

Proper Labeling of the investigational device

On the Investigational device or its immediate package

Capable Manufacturing Company, Inc.
Contents: 1 Smart Checker

CAUTION—Investigational device.
Limited by Federal (or United States)
law to investigational use.

- the name and place of business of the manufacturer, packer, or distributor;
- the quantity of contents, if appropriate; and
- the statement, **"CAUTION Investigational device. Limited by Federal (or United States) law to investigational use**."
- The label must also describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.
- must not contain any false or misleading statements nor imply that the device is safe or effective

Sponsor Responsibilities-Overview
21 CFR 812 Subpart C

- Ensuring proper monitoring of the investigation
- Ensuring that IRB review and approval are obtained
- Ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation.
- Submitting an IDE application to FDA (SR only)

Sponsor Responsibilities
RECORDS 812.140

Accurate and complete records:

Signed investigator agreements

Records concerning complaints and adverse device effects

All Correspondence (SR)

Shipment and disposition of the device (SR)

Any other records that FDA requires (SR)

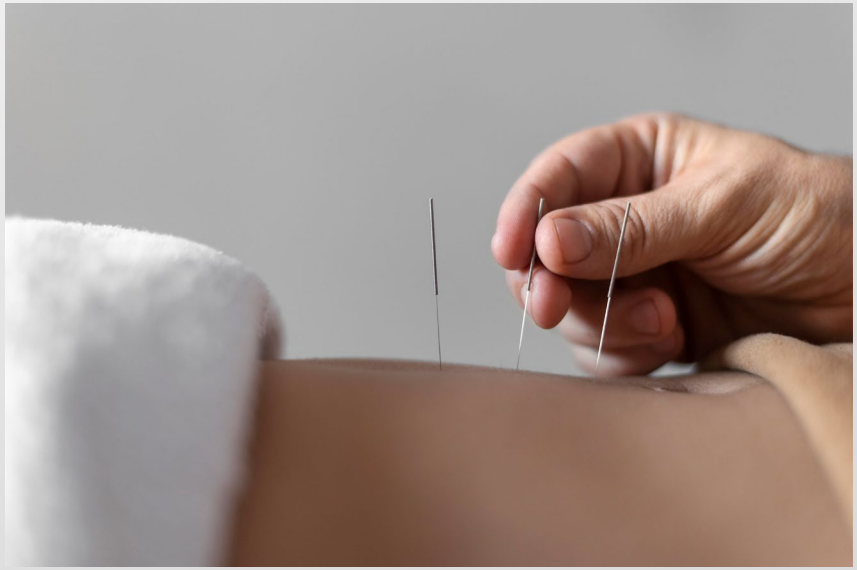
Sponsor Responsibilities
REPORTS 812.150

Unanticipated adverse device effects

What is an Unanticipated Adverse Device Effect (UADE)?

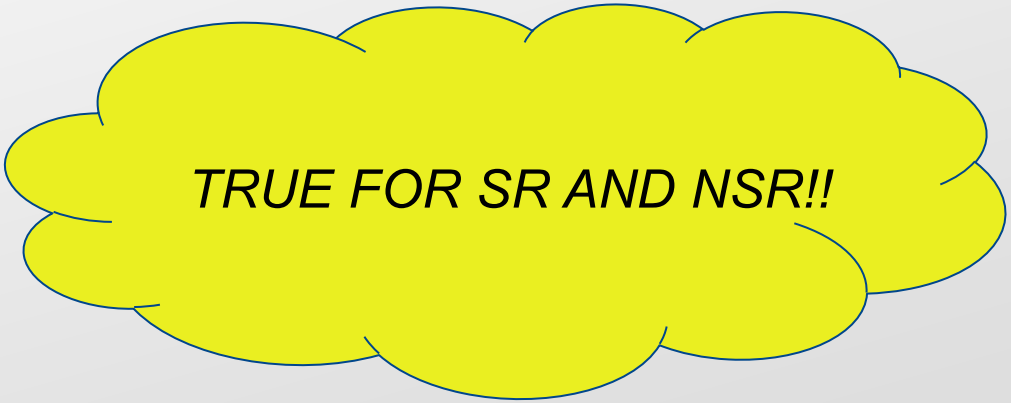
812.3: Unanticipated adverse device effect means

Any **serious adverse effect** on health or safety or any life-threatening problem or death **caused by, or associated with, a device**, if that effect, problem, or death **was not previously identified in nature, severity, or degree of incidence** in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.



Sponsor Responsibilities
REPORTS 812.150

Sponsors must EVALUATE any UADE and report results of evaluation to IRB and FDA



Sponsor Responsibilities –Subpart C
REPORTS

WHAT DO I REPORT	TO WHOM
UADE Evaluation Report*	To FDA and IRB within 10 working days of learning of UADE
Withdrawal of IRB approval *	To FDA, IRB, and other investigators within 5 working days
Recall and device disposition*	To FDA and IRB within 30 working days
Lack of Informed Consent*	To FDA within 5 working days

*NSR and SR

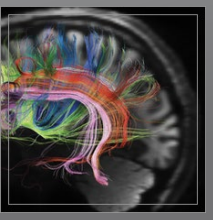
Sponsor Responsibilities –Subpart C
REPORTS

WHAT DO I REPORT	TO WHOM
Progress Reports *	At least yearly--To IRB* (NSR and SR) and FDA (SR)
Final Report(*)	Notify FDA w/30 days of completion or termination; submit report to FDA and IRB within 6 months after termination or completion FOR NSR DEVICE STUDIES—FINAL REPORT WITHIN 6 MONTHS TO IRB

*NSR and SR

Sponsor Responsibilities –Subpart C
REPORTS

WHAT DO I REPORT	TO WHOM
Withdrawal of FDA approval (SR)	To IRB, and investigators within 5 working days
Current Investigator List (SR)	To FDA every 6-months unless waiver granted
Significant Risk Device Determinations (NSR)	To FDA within 5 working days




Investigator Responsibilities

Investigator Responsibilities—21 CFR 812 Subpart E

- 812.100: General Responsibilities

"An investigator is responsible for ensuring that an investigation is **conducted according to the signed agreement, the investigational plan and applicable FDA regulations,** for **protecting the rights, safety, and welfare of subjects under the investigator's care**, and for the **control of devices under investigation**. An investigator also is responsible for ensuring that **informed consent** is obtained in accordance with **part 50** of this chapter. Additional responsibilities of investigators are described in subpart G."

Investigator Responsibilities – 21 CFR 812.110

- Implement only after IRB and FDA approval
- Follow the Investigator's Agreement, the protocol, sponsor requirements, and FDA regulation
- Use the device only on subjects in your study
- Dispose of the device at the end of the study per sponsor's direction (returning or disposing)
- Disclose financial interests to the Sponsor (SR device studies where applicable)

Investigator Responsibilities –Subpart G
RECORDS 21 CFR 812.140

A**ccurate and complete records**:

Records of each subject's **case history and exposure** to the device

Proof of Informed Consent or documentation as to why not. (SR and NSR)

All relevant observations (e.g., ADEs, condition of each subject) (SR only)

A record of the **exposure of each subject to the investigational device**, including the date and time of each use, and any other therapy. (SR only)

Investigator Responsibilities –Subpart G **RECORDS** 21 CFR 812.140 **(cont'd)**

The investigator must maintain **accurate and complete records** relating to the investigation. These records include:

All Correspondence (SR)

Receipt, Use, and Disposition of the device (SR) that relate to:

The **type and quantity of the device**, the **dates of its receipt**, and the **batch number** or code mark.

The **names of all persons who received, used, or disposed of each device**.

Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of..

Investigator Responsibilities –Subpart G RECORDS (cont'd)

The protocol, with documents showing the dates of and reasons for each deviation from the protocol.

Any other records that FDA requires

Investigator Responsibilities –Subpart G
REPORTS Sec. 812.150 Reports

WHAT DO I REPORT	TO WHOM
UADEs*	To Sponsor within 10 working days (NOTE: IRB Reporting requirements are different)
Withdrawal of IRB approval *	To Sponsor within 5 working days
Lack of Informed Consent*	To sponsor and IRB within 5 working days
Other*	Whatever the IRB or FDA Wants

*NSR and SR

Investigator Responsibilities –Subpart G
REPORTS Sec. 812.150 Reports

WHAT DO I REPORT	TO WHOM
Progress Reports (SR)	At least yearly--To Sponsor, Monitor, and IRB
Deviations from Investigational Plan for Emergencies (SR)	To Sponsor and IRB soon as possible and no later than 5 working days
Final Report (SR)	To Sponsor and IRB within 3 months after termination or completion

Investigator Responsibilities –Subpart G
INSPECTIONS Sec. 812.145 Inspections

Allow FDA to come in and inspect.

Allow FDA to inspect records identifying subjects.

Changes to the Plan—Joint Sponsor and Investigator Effort at NIH (SR Device Studies)

When there are changes to your protocol, manufacturing, or plan, notify your sponsor and regulatory specialists.

Changes requiring prior approval SUPPLEMENT to the FDA

(30 day clock)

- Affecting the validity of data/information,
- Patient risk to benefit relationship,
- Scientific soundness of investigational plan,
- Right, safety or welfare of subjects.
- Developmental Changes that present a significant change in design or basic principle of operation

Changes to the Plan—Joint Sponsor and Investigator Effort at NIH

Changes effected for emergency use.
Such deviation shall be reported to FDA within 5-working days after the sponsor learns of it (see 812.150(a)(4))

Changes to the Plan (cont'd)

Notice of IDE Change

Submit to FDA within 5 days of change being made
On the basis of credible information

Developmental changes. that do not constitute a significant change in design or basic principles of operation and that are made in response to information gathered during the course of an investigation.

Changes to clinical protocol.
that do not affect:

A. The validity of the data or risk to benefit ratio;
B. The scientific soundness of the investigational plan; or
C. The rights, safety, or welfare of the human subjects

Changes to the Plan (cont'd)

Changes submitted in annual report.

Minor changes that do not affect validity of the data, scientific soundness of the study, and the rights, safety, or welfare of the subjects.

Key Points

Sponsors and Investigators have important roles in device research

Know your responsibilities

Reach out to the IRB and regulatory professionals in your IC for guidance

Thank you