Understanding when Assays become Investigational Assays
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Objectives

- Understand the different stages of assay development and apply the applicable regulatory framework, specifically investigational devices regulations.
- Accurately complete the IRBIS application, assay tables, and consent forms to facilitate IRB review processes.
- Evaluate when a modification occurs and how it will impact the regulatory framework and IRB requirements

What makes a device a MEDICAL DEVICE?

1. recognized in the official National Formulary, or the United States Pharmacopoeia, 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
4. 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.

https://www.fda.gov/medical-devices/classify-your-medical-device/how-determine-if-your-product-medical-device

What makes a device a MEDICAL DEVICE?

Consideration 1: Is there a device?

Consideration 2: Is the device intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease?

If yes to both, the device in the study is a “medical device.”

NOTE: This is only about the device, not necessarily about how it is being used in the study.

What is MEDICAL DEVICE?

- CT scanners
- ECGs
- Wheelchairs
- Laparoscopes
- Robots
- Virtual reality systems (sometimes)
- Pacemakers
- Mobile Apps (sometimes)
- Electric toothbrushes
- Catheters
- Stents
- In vitro diagnostic kits
- Sutures
- Software (sometimes)
- Algorithms (sometimes)
- Blood tests (sometimes)
- Genetic tests (sometimes)

What makes a study an Investigational MEDICAL DEVICE STUDY?

I.e., FDA regulated

Once a medical device in the study has been identified, are ANY of the following true?

- The study evaluates the safety or effectiveness of a device in one or more persons
- Data from the study regarding participants or controls will be submitted to or held for inspection by FDA as part of application for a research or marketing permit
- Data regarding use of a device on human specimens will be submitted or held for inspection by FDA as part of application for research or marketing permit.

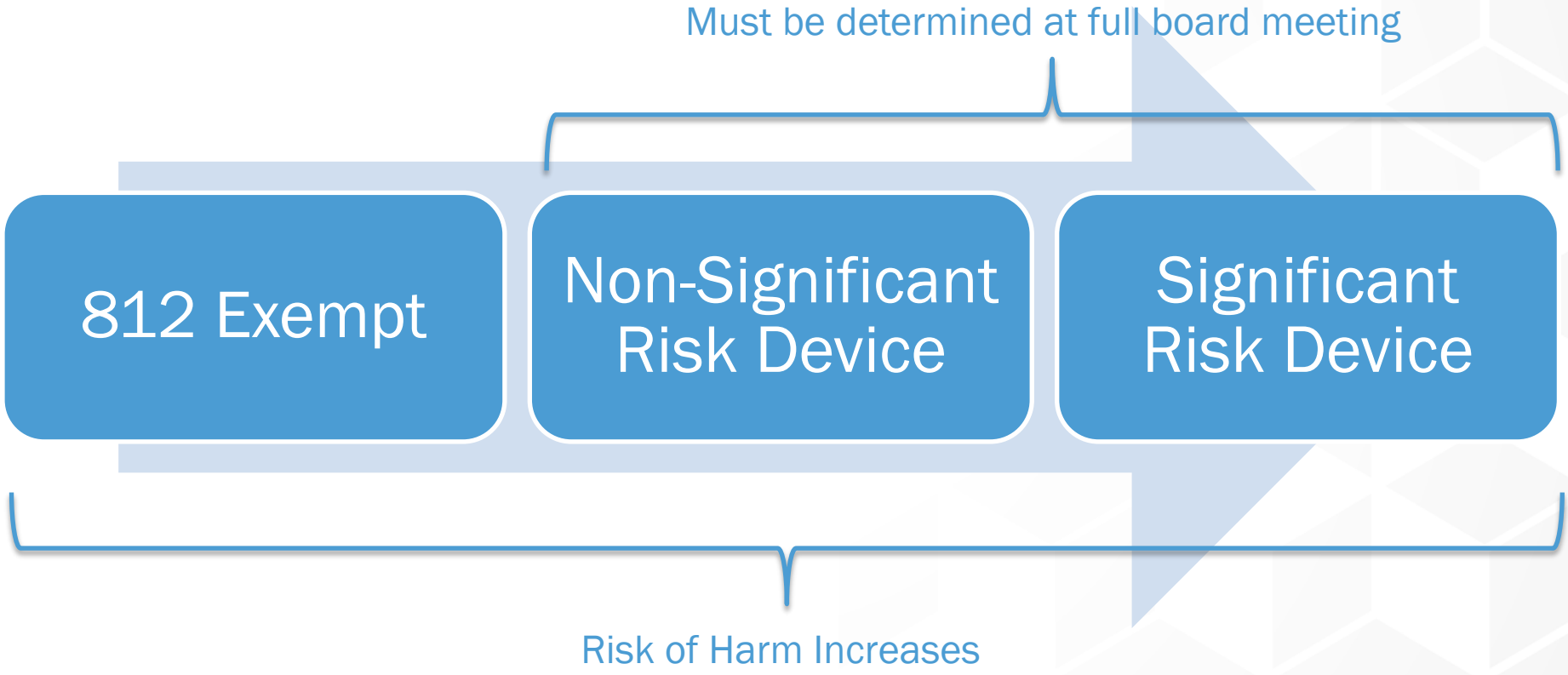
What makes a study an Investigational MEDICAL DEVICE STUDY?

I.e., FDA regulated

The medical device is being studied by either of the following:

- Evaluating the safety of the medical device
  - Safety assessment are more common with physical devices or sampling method to assess their physical risks
  - E.g. incidence of adverse events
- Evaluating the effectiveness of the medical device
  - Testing the ability of the device to potentially be used in the future as a medical device.
  - **Does not mean they are using the research results in clinical care**. There are other ways to test effectiveness.
  - E.g. outcomes, correlation between unapproved device results and gold standard results, outcome of investigational medical device and action that was taken in clinical care **evaluated as a medical chart review.**

Classification of Devices



SR (Significant Risk Device)

Under 21 CFR 812.3, if one of the following is true for the investigational device:

- Intended use as an implant or 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

What should the determination be?

A study is determining the safety and effectiveness of dissolvable sutures

What should the IRB consider for a determination?

What are your device findings?

NSR (Non-Significant Risk Device)

Under 21 CFR 812.3, an NSR device study is one that does not meet the definition for an SR device study.

* Reminder- An NSR determination does not meet minimal risk and should not be confused with expedited/minimal risk.

What should the determination be?

A study is determining the safety and effectiveness of a Urethral Occlusion Device for less than 14 days.

What should the IRB consider for a determination?

What are your device findings?

812 Exempt (IDE Exempt)

1. Device other than transitional device in commercial distribution before 5/28/1976.

2. Devices introduced after 5/28/1976 that the FDA has determined to be substantially equivalent to devices in #1 or being used in accordance with its approved labeling.

3. A device undergoing consumer preference testing, testing of a modification or testing of two or more devices in commercial distribution if not for the purpose of determining safety or effectiveness.

4. Animal Device

5. Custom device, unless the device is being used to determine safety or effectiveness for commercial distribution.

812 Exempt Continued

6. Diagnostic Device Testing Exemption-All Criteria Must be met:
   a) Is noninvasive,
   b) Does not require an invasive sampling procedure that presents significant risk
   c) Does not by design/intention introduce energy into a subject
   d) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established product or procedure.
      - Research test and standard must be the same. It can be confirmed by conducting the standard test in the research, comparing to test in medical record, etc.
      - Trying to avoid taking clinical action with a results from a test where the effectiveness is not established.

Assay Study

A COVID assay is being tested to see if its effective as a diagnostic.

Is this an FDA regulated study?

What are your device findings?

510k Clearance

A 510(k) is a pre-market submission made to the FDA for the purpose of demonstrating to the FDA that the device to be marketed is at least as safe and effective, (that is, substantially equivalent) to a legally marketed device.

- If a 510(k) submission is pending the device is still considered investigational
- If 510(k) cleared but a new use is being studied, IDE regulations will apply and a device determination would still be required.
- If the 510(k) approved use of a device is being studied, an 812 exemption can be given.

Identifiable Information and Assay Development

- Generally, utilization of secondary bio-specimens that are de-identified before receipt by the study team is considered NHSR.
  - The one exception is Assay Development per FDA guidance, if you are testing an in vitro diagnostic assay than this is considered Human Subject Research regardless of identifiability.
    - Applicable for 812 exempt, NSR, SR

Assay Table, IRBIS Application, and Consent Form

Classification of Assays

Must be determined at full board meeting

Not FDA Regulated Study	812 Exempt	Non-Significant Risk Device	Significant Risk Device
-Not studying as a diagnostic	-Studying as a diagnostic, confirming results if not approved	-Studying as a diagnostic, not confirming results if lacking approval -Meets NSR Def/slide 11	-Studying as a diagnostic, not confirming results if lacking approval -Meets SR Def/slide 9

Risk of Harm Increases

812 Reminder

6. Diagnostic Device Testing Exemption-All Criteria Must be met:
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   d) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established product or procedure.
      - Research test and standard must be the same. It can be confirmed by conducting the standard test in the research, comparing to test in medical record, etc.
      - Trying to avoid taking clinical action with a results from a test where the effectiveness is not established.

Collection Mechanism	Collection Mechanism Notes/Approval (e.g. utilized for all types of samples, self-collection, or ml's, or past the nares)	Assay being run on collection (state assay)	EUA/or FDA Approved (please provide any additional details.	Results being returned to patient, in patients' medical record, or for any additional action/follow-up	If being returned in any way, are they being confirmed and if so, with what (provide FDA EUA Status)?	Are you testing safety or effectiveness of assay or collection methodology	Risk/Reg	Determi-nation
Blood drawing	**SST** (8.5mL tubes; total of 17mL at each visit) for assay during visits 1, 2, 3 and 4 (each visit is one day apart)	Neutralizing antibody (nAb)	EUA	Yes	NA as has EUA status	No	Overall blood volume-greater than minimal (OHRP) Approved and not for S/E FDA	Not FDA Regulated
Blood drawing	**SST** (8.5mL tubes; total of 17mL at each visit) for assay during visits 1, 2, 3 and 4 (each visit is one day apart)	Neutralizing antibody (nAb)		No		No	Overall blood volume-greater than minimal (OHRP) Not Returning results or for S/E	Not FDA Regulated
Blood drawing	**SST** (8.5mL tubes; total of 17mL at each visit) for assay during visits 1, 2, 3 and 4 (each visit is one day apart)	Neutralizing antibody (nAb)	EUA	Yes	NA as has EUA status	Yes	Overall blood volume-greater than minimal (OHRP) Approved and for S/E	FDA Regulated 812 Exempt

Collection Mechanism	Collection Mechanism Notes/Approval (e.g. utilized for all types of samples, self-collection, or ml's, or past the nares)	Assay being run on collection (state assay)	EUA/or FDA Approved (please provide any additional details.	Results being returned to patient, in patients' medical record, or for any additional action/follow-up	If being returned in any way, are they being confirmed and if so, with what (provide FDA EUA Status)?	Are you testing safety or effectiveness of assay or collection methodology	Risk/Reg	Determi-nation
Blood drawing	**SST** (8.5mL tubes; total of 17mL at each visit) for assay during visits 1, 2, 3 and 4 (each visit is one day apart)	Neutralizing antibody (nAb)		No. Results will not be given to participants	NA	Yes	Overall blood volume-greater than minimal (OHRP) Not returning Results FDA	FDA Regulated 812 Exempt as not returning results
Blood drawing	**SST** (8.5mL tubes; total of 17mL at each visit) for assay during visits 1, 2, 3 and 4 (each visit is one day apart)	Neutralizing antibody (nAb)		Yes	Confirmed with FDA EUA Test	Yes	Overall blood volume-greater than minimal (OHRP) Returning Results FDA	FDA Regulated 812 Exempt as Confirming results
Blood drawing	**SST** (8.5mL tubes; total of 17mL at each visit) for assay during visits 1, 2, 3 and 4 (each visit is one day apart)	Neutralizing antibody (nAb)		Yes	No	Yes	Overall blood volume-greater than minimal (OHRP) Returning Results (FDA)	SR or NSR Consider design, what could occur if test incorrect. (e.g.pop)

IRBIS Selection

>> A.4.A. Biomedical methods and procedures Reference ID: 182460

Online Submission FAQ | Online Submission Guide

Current Application: Quick View (HTML) | PDF | Delete Submission

5. When the intent of a clinical investigation is to collect information about the safety or effectiveness of a device, the need for an Investigational Device Exemption (IDE) must be evaluated. Please review the Investigational Device Guidance document prior to completing this section. Your response to the following questions will determine if an IDE is needed.

A. Select the response that best describes your investigation: *

- (●) 1. This research is **investigator-initiated** and is designed to study one of the following:
  - An unapproved device (includes assays [e.g. in vitro diagnostics], software, algorithms and some mobile applications.)
  - An approved device with unapproved components
  - A new indication for an approved device **even if no marketing application is planned**
- ( ) 2. This research is designed to support an IDE (device marketing application).
- ( ) 3. This research is designed to collect safety and/or effectiveness information about a device.
- ( ) 4. The device(s) in this research is being **used as "tool"** to address a research question, collect information or test a physiologic principle. No data is collected about the device itself.
- ( ) 5. None of the above.

Required document(s): Device Description

B. Depending on the characteristics of the investigational device and the investigation, the investigation may fall into one of four categories. Please select one of the following: *

- ( ) 1. I have obtained an IDE# for this investigation.
  Please note: The IRB will not review your submission unless the FDA has been in receipt of your IDE application at least 30 days and you have correspondence indicating that the investigation has not been placed on hold.
- ( ) 2. The FDA has determined that this investigation represents Non-Significant Risk
- ( ) 3. The FDA has determined that this investigation is exempt from IDE regulations
- (●) 4. have not submitted an application to the FDA. I am requesting that the IRB approve my request for an exemption from the IDE regulation OR make a non-significant risk (NSR) determination.

C. You have indicated that your investigation is either exempt from IDE requirements or is a not significant device (NSR) investigation. Please select one of the following: *

- (●) 1. I would like to apply for an exemption from the IDE requirements.
- ( ) 2. I (or the device manufacturer) have made an initial determination that the device as used in this investigation, meets the criteria for a non-significant risk device.

Consent Form Requirements

- Consent Forms have to say if it's an investigational device, and explain FDA status;
- Non-Assay Suggested Language
  - This device is approved by the FDA and being used within that approval for this study.
  - This device is approved by the FDA, however, is being used for a new indication.
  - This device is investigational and has not been approved by the FDA.
- Assay Suggested Language
  - The test being used is investigational and has not been approved by the FDA for this purpose.

Select One

- The results of this test will not be returned to you and will not influence your care.
- The results of this test will be returned to you and your physician will discuss how the results may be utilized or what other testing may be appropriate

IRB's Role and Considerations

What is the IRB's Role?

The IRB is designated by the FDA to make the device determination, regardless of the sponsor's or the Principal Investigator's determination.

If the IRB is unsure of the device determination, the FDA can provide consultation and a final determination.

What does the IRB need to consider?

If FDA hasn't already made the risk determination, then it's up to the IRB to decide whether it concurs with the sponsor's or PI's risk assessment. The IRB may disagree with the sponsor's or PI's assessment. Here are some key items the IRB will consider:

- The basis for the risk determination
- The type of harm that may result from use of the device
- Any additional procedures a study subject may need to undergo as part of the study (the IRB must assess the potential harm of the procedure as well as of the device itself)

What does the IRB need to do?

1. Make a device determination for each device in the study.
   a) Document in the minutes the determination for each device
   b) Include any relevant discussion regarding risk and the boards analysis

If SR Device

1. Notify sponsor and investigator of SR decision.
2. The IRB can approve the study as greater than minimal risk with the condition that the study may not commence until an IDE has been provided by the FDA.
3. After IDE obtained by sponsor, the IDE can be submitted to the IRB and human subject research can begin after final approval.

If NSR Device

1. Proceed to review study as normal, as greater than minimal risk study (Full Board), as an IDE is not required

If 812 Exempt Device

1. Proceed to review study as normal, may consider minimal risk (Expedited Cat 1.) depending upon remaining research activities.

Modifications

Tips and Tricks-Modifications

When does an assay need to be re-assessed by the IRB?

- Safety or Effectiveness/Design Changes
- Returning Results
- FDA Approval or EUA Status Changes

How do I tell the IRB that the above has changed?

- Identify in the Modification submission that your assay table has been updated or been included for review.
- Replace the previous assay table or provide an initial table as an attachment
- If you are now testing safety/effectiveness please update the device section in IRBIS as outlined in slide 23
- Adjust consent language if applicable as outlined in slide 24

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