Best Practices for the Preparation, Submission, and Maintenance of Sponsor-Investigator INDs and IDEs:

The Investigational Device Exemption (IDE) Workshop

PART 1: Medical Device Studies and the IDE

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ReGARDD

- Regulatory Guidance for Academic Research of Drugs and Devices (ReGARDD) is comprised of regulatory affairs specialists from North Carolina institutions that receive funding from the NIH Clinical and Translational Science Awards (CTSA).
  - UNC and RTI: NC TraCS
  - Wake Forest
  - Duke
- Mission is to provide researchers with the tools and resources necessary to find the successful pathway from discovery to clinical implementation of new and innovative drugs, biologics, medical devices, and/or therapies.
- Website: www.regardd.org

ReGARDD

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PART 1: Medical Device Studies and the IDE

- Definitions and Marketing Overview
- Pre-Submission Meetings
- Clinical Investigations of a Medical Device
- IDE Exemption
- SR/NSR Determination and the IDE

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What is a Medical Device?

Section 201(h) of the FD&C Act

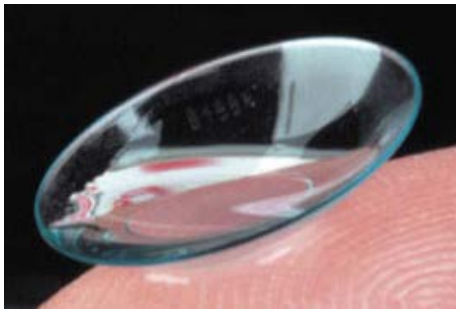
An instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent or other similar or related article or component part or accessory which:

- is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease

- is intended to affect the structure or any function of the body

- does not achieve any of 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 any of its primary intended purposes

What is a Medical Device?



Food and Drug Administration

- Center for Devices and Radiological Health (CDRH) is the center responsible for overseeing:
  - Medical devices*
  - Radiation-emitting products (medical and non-medical, e.g., lasers, ultrasound equipment, microwave ovens, tanning beds)
  - Combination products, when the primary mode of action is the device component

*Medical devices used to safeguard blood, blood components, and cellular products from infectious agents are regulated by CBER

Medical Device Regulation

Medical Device Amendments (1976):

- Prior to 1976, investigational devices were either not reviewed or reviewed as drugs
- Established device classifications based on risk
- Established the Investigational Device Exemption (IDE)

Medical Device Classification

- The FDA has established three regulatory classes of devices based on the level of control necessary to assure the safety and effectiveness of the device:
  - Class I: General Controls (low risk)

    Example: dental floss, medical scissors, dental syringe
  - Class II: General Control & Special Controls (moderate risk)

    Example: powered wheel chair, MRI, clinical mercury thermometer
  - Class III: General Controls and Premarket Approval (high risk)

    Example: external defibrillator, replacement heart valves

General Controls

For All Medical Devices

- Establishment Registration (21 CFR 807.20)
- Medical Device Listing (21 CFR 807.20)
- Manufacturing in accordance with Quality System Regulation (21 CFR 820)
- Labeling (21 CFR 801 or 809)
- Medical Device Reporting (21 CFR 803)
- Submission of a premarket notification (510(k))
- Investigational Device Exemption (21 CFR 812)

Special Controls

For Class II Medical Devices

- Performance standards
- Post-market surveillance
- Patient registries
- Special labeling requirements
- Premarket data requirements
- Guidelines

Premarket Approval

For Class III Medical Devices

- Premarket approval (PMA) is a **marketing application** for Class III medical devices.
  - Scientific and regulatory review that evaluates the safety and effectiveness of the device.
- Due to the level of risk, FDA has determined that general and special controls are insufficient to assure the safety and effectiveness of Class III devices.

Commercialization Options

- Exempt - most Class I (about 95%) and a few Class II (about 9%) devices are exempt from the 510(k) regulations
- 510(k) - device is at least as safe and effective, or substantially equivalent to, a legally marketed device (predicate) that is not subjected to a PMA
    - 90 day FDA review
- PMA - premarket approval is required for all Class III devices. Focus on scientific and regulatory review of safety and effectiveness
    - 180 day FDA review

Commercialization Options

	Clinical Studies?
• Exempt - most Class I (about 95%) and a few Class II (about 9%) devices are exempt from the 510(k) regulations	Unlikely
• 510(k) - device is at least as safe and effective, or substantially equivalent to, a legally marketed device (predicate) that is not subjected to a PMA • 90 day FDA review	Sometimes (10-15%)
• PMA - premarket approval is required for <u>all Class III</u> devices. Focus on scientific and regulatory review of safety and effectiveness • 180 day FDA review	Almost always

How do I know my device classification and the correct commercialization path?

Medical Device Classification

- Device classifications are grouped according to medical specialties.
  - 16 groups
  - Code of Federal Regulations: 21 CFR 862-892

862 Clinical Chemistry and Clinical Toxicology
864 Hematology and Pathology
866 Immunology and Microbiology
868 Anesthesiology
870 Cardiovascular
872 Dental
874 Ear, Nose, and Throat
876 Gastroenterology and Urology
878 General and Plastic Surgery
880 General Hospital and Personal Use
882 Neurology
884 Obstetrical and Gynecological
886 Ophthalmic
888 Orthopedic
890 Physical Medicine
892 Radiology

Medical Device Classification

Subpart D—CARDIOVASCULAR PROSTHETIC DEVICES

§870.3250	Vascular clip.
§870.3260	Vena cava clip.
§870.3300	Vascular embolization device.
§870.3375	Cardiovascular intravascular filter.
§870.3450	Vascular graft prosthesis.
§870.3460	Endovascular Suturing System.
§870.3470	Intracardiac patch or pledget made of polypropylene, polyethylene terephthalate, or polytetrafluoroethylene.
§870.3535	Intra-aortic balloon and control system.
§870.3545	Ventricular bypass (assist) device.
§870.3600	External pacemaker pulse generator.
§870.3605	Pacing system analyzer.
§870.3610	Implantable pacemaker pulse generator.
§870.3620	Pacemaker lead adaptor.
§870.3630	Pacemaker generator function analyzer.
§870.3640	Indirect pacemaker generator function analyzer.
§870.3650	Pacemaker polymeric mesh bag.
§870.3670	Pacemaker charger.
§870.3680	Cardiovascular permanent or temporary pacemaker

Medical Device Classification

ELECTRONIC CODE OF FEDERAL REGULATIONS

View past updates to the e-CFR.
Click here to learn more.

e-CFR data is current as of October 30, 2015

Title 21 → Chapter I → Subchapter H → Part 870 → Subpart D → §870.3945

Browse Previous

Title 21: Food and Drugs
PART 870—CARDIOVASCULAR DEVICES
Subpart D—Cardiovascular Prosthetic Devices

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§870.3945 Prosthetic heart valve sizer.

(a) *Identification.* A prosthetic heart valve sizer is a device used to measure the size of the natural valve opening to determine the size of the appropriate replacement heart valve.

(b) *Classification.* Class I (general controls). The device is exempt from the premarket notification procedures in subpart E of part 807 of this chapter subject to the limitations in §870.9.

Medical Device Classification

ELECTRONIC CODE OF FEDERAL REGULATIONS

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e-CFR data is current as of October 29, 2015

Title 21 → Chapter I → Subchapter H → Part 870 → Subpart D → §870.3450

Browse Previous | Browse Next

Title 21: Food and Drugs
PART 870—CARDIOVASCULAR DEVICES
Subpart D—Cardiovascular Prosthetic Devices

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§870.3450 Vascular graft prosthesis.

(a) *Identification.* A vascular graft prosthesis is an implanted device intended to repair, replace, or bypass sections of native or artificial vessels, excluding coronary or cerebral vasculature, and to provide vascular access. It is commonly constructed of materials such as polyethylene terephthalate and polytetrafluoroethylene, and it may be coated with a biological coating, such as albumin or collagen, or a synthetic coating, such as silicone. The graft structure itself is not made of materials of animal origin, including human umbilical cords.

(b) *Classification.* Class II (special controls). The special control for this device is the FDA guidance document entitled "Guidance Document for Vascular Prostheses 510(k) Submissions."

Vascular Prosthesis Guidance Document: Risks and Controls

RISK	CONTROLS
2. Leakage a. Hematoma b. Hemorrhage c. Blood Leakage (from failure to clot)	**510(k)** Conduct all appropriate tests specified in ANSI/AAMI VP20-1994, Section 5.2 (Porosity, Water Permeability, Integral Water Permeability/Leakage, and/or Water Entry Pressure).
	Conduct (**in vivo**) preclinical and/or clinical evaluations of devices incorporating new or substantially modified materials or design, in accordance with ANSI/AAMI VP20-1994, Section 6 (Requirements for In Vivo Preclinical and Clinical Evaluation); when the risk cannot be assessed solely through **in vitro** testing.
	Labeling - Instructions for Use Provide labeling in accordance with ANSI/AAMI VP20-1994, Section 4.6 (General Information and Instructions for Use), Section 4.1 (Configuration and Size Designation), Section 4.2 (Intended Clinical Use Designation), and information, as appropriate, in accordance with Section 4.8 (Marking).
	Provide instructions for proper pre-clotting of the graft (if applicable) and use of hemostatic agents (if applicable).
	State that potential complications associated with vascular grafts include leakage (which may occur in conjunction with hematoma, hemorrhage, and blood leakage from failure to clot).
	Include a summary of the clinical studies, if clinical studies were submitted in the 510(k).

RISK	CONTROLS
3. Biocompatibility Allergic Reaction	**510(k)** Address the issue of biological safety in accordance with FDA biocompatibility guidance and ANSI/AAMI VP20-1994, Section 4.4 (Biocompatibility and Biostability).
	Conduct (**in vivo**) preclinical and/or clinical evaluations of devices incorporating new or substantially modified materials or design, in accordance with ANSI/AAMI VP20-1994, Section 6 (Requirements for In Vivo Preclinical and Clinical Evaluation); when the risk cannot be assessed solely through **in vitro** testing.
	Labeling - Instructions for Use Contraindicate device use for patients with known sensitivity to device material.
	Include a summary of the clinical studies, if clinical studies were submitted in the 510(k).

http://tinyurl.com/l6htwcq

Medical Device Classification

ELECTRONIC CODE OF FEDERAL REGULATIONS

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Click here to learn more.

e-CFR data is current as of October 30, 2015

Title 21 → Chapter I → Subchapter H → Part 870 → Subpart D → §870.3925

Browse Previous | Browse Next

Title 21: Food and Drugs
PART 870—CARDIOVASCULAR DEVICES
Subpart D—Cardiovascular Prosthetic Devices

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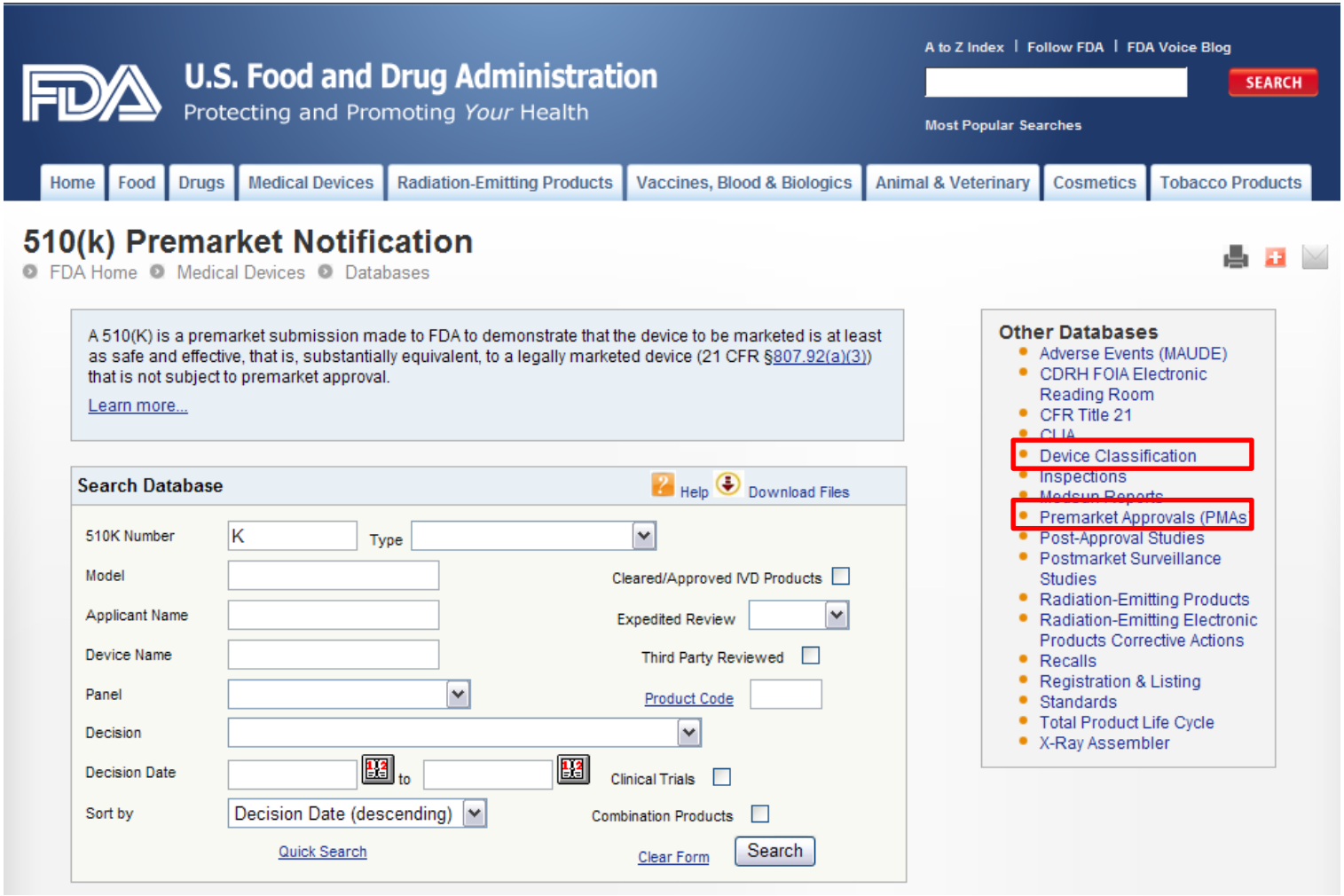
§870.3925 Replacement heart valve.

(a) *Identification.* A replacement heart valve is a device intended to perform the function of any of the heart's natural valves. This device includes valves constructed of prosthetic materials, biologic valves (e.g., porcine valves), or valves constructed of a combination of prosthetic and biologic materials.

(b) *Classification.* Class III (premarket approval).

Medical Device Classification



510(k) Process

- Marketing "Clearance" application
- Allows FDA to determine **substantial equivalence**:
  - Demonstration that a new device, as compared to a predicate device, has:
    - The same intended use; **AND**
    - The same technological characteristics; **OR**
    - Differences in technological characteristics do not raise different questions regarding safety and effectiveness

What is a Predicate Device?

- A legally marketed Class I or II device that is used for comparison to a new device for the purpose of determining substantial equivalence (21 CFR 807.92(a)(3)).

- You need to demonstrate to FDA that your device is just as safe and just as effective as the FDA-cleared predicate.

What does “Intended Use” mean?

- **Intended Use**
  - general purpose of the device or its function, and encompasses the indications for use

- **Indication for Use**
  - describes the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended

Intended Use Examples

- **Same Intended Use:**
  - Assay to detect H. pylori in adults
  - Assay to detect H. pylori in children
- **Different Intended Use:**
  - Laser ablation to kill tumor cells
  - Laser ablation to treat epilepsy

Technological Characteristics

- Design, materials, chemical composition, energy source
- Can also have a “reference” device with similar technological characteristics but a different intended use
  - This will help inform technological risks and necessary testing

510(k) Process

- Marketing "Clearance" application
- Allows FDA to determine **substantial equivalence**:
  - Demonstration that a new device, as compared to a predicate device, has:
    - The same intended use; **AND**
    - The same technological characteristics; **OR**
    - Differences in technological characteristics do not raise different questions regarding safety and effectiveness

What if my device is novel, but not high risk?

- **De novo process:** provides a pathway for Class I (low risk) and Class II (moderate risk) medical devices for which general controls or general and special controls provide a reasonable assurance of safety and effectiveness, but for which there is no legally marketed predicate device
- Can be submitted after a 510(k) NSE determination, or initially
- You must understand and explain all known risks and benefits of the device
  - How will device risks be mitigated?
  - How will device effectiveness be assured through general/special controls?
- 120 day review by FDA

PART 1: Medical Device Studies and the IDE

- Definitions and Marketing Overview
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Q-Sub Program: Pre-Submission Meeting

- A pre-submission is defined as a formal written request from an applicant for feedback from FDA to be provided in the form of a formal written response or a meeting/teleconference.
- Can be utilized for a wide range of questions
- Meeting will be held 75-90 days after the request is received

Q-Submission Guidance:
http://tinyurl.com/kvbf54z

Pre-Submission Meeting

- Mechanism to obtain feedback from FDA on protocols and other aspects of device development
  - Similar to pre-IND for drugs/biologics
- Written submission that includes:
  - device description, intended use information, clinical protocol or development plan, and questions
- Encouraged, but not required, by FDA
- Can be used even if no clinical study will follow
- Can be used more than once
  - Unlike the formal meeting schedule in drug development

Pre-Submission Meeting

- Recommended contents of a pre-sub meeting package:
  - Cover letter
  - Table of Contents
  - Device Description
  - Proposed Intended Use
  - Previous Discussions or Submissions
  - Product Development
  - Specific Questions
  - Mechanism for Feedback
  - Other Logistical Information

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What is a Clinical Investigation?

- A clinical Investigation is any experiment in which a drug or **device** is administered, dispensed to, or used involving, one or more human subjects, except for the use of a marketed product in the course of medical practice.
  - This would include clinical studies in which a subject is assigned to specific intervention according to a study protocol.

Who Conducts a Clinical Investigation?

- Sponsor: An individual, company, academic institution, or other organization that **takes responsibility** for and **initiates** a clinical investigation.
- Investigator: An individual who **conducts** a clinical investigation, i.e., under whose **immediate direction** a device is used.
- Sponsor-Investigator: An individual who both **initiates** and **conducts** an investigation, and under whose **immediate direction** a device is used.

When is a Clinical Investigation a "Device Study"?

- If the objective of the clinical investigation is to assess the **safety** and/or **effectiveness** of a medical device, then the study is a device study and is subject to regulatory oversight by the US Food and Drug Administration (FDA).
- 21 CFR 812 (Investigational Device Exemption)

What is an Investigational Device Exemption (IDE)?

- An IDE is a **regulatory submission** to the FDA that permits the clinical investigation of devices.
- An approved IDE allows:
  - an investigational device to be used in a clinical study in order to collect safety and effectiveness data.
  - a device to be shipped lawfully for the purpose of conducting clinical investigations.

Are all clinical investigations that use devices subject to regulatory oversight by FDA?

- No. If the objective of the study is not to test the safety or effectiveness of the device, then the study would not fall within the scope of 21 CFR 812.
- Devices used as “tools”

Clinical Investigation of a Medical Device

- Objective of the study is to assess the safety or effectiveness of the device

Be exempt of the IDE regulations
(21 CFR 812.2 (c))

Have an approved IDE
a) abbreviated IDE (21 CFR 812.2 (b)) b) IDE (21 CFR 812.20)

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Investigations Exempt from the IDE Regulations

- A legally marketed device when used in accordance with its labeling.
- A diagnostic device meeting 4 specified criteria.
- A device undergoing a consumer preference testing, testing of 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.
- A device intended solely for veterinary use.
- A device for research on or with laboratory animals.
- A custom device. *(21 CFR 812.3(b)) (http://tinyurl.com/lbxl9k8)*

In Vitro Diagnostics (IVD)

- IVDs are those reagents, instruments, and systems intended for use in diagnosis of disease or other conditions.
- Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body.
  - Blood, spinal fluid, tissue samples, serum, urine
- The FDA considers the IVD to be the entire process from specimen collection to results reporting:
  - Specimen collection and transport
  - Specimen preparation
  - Specimen examination/analysis
  - Method of calculating/reporting result

Diagnostic Exemption Criteria

- Per 21 CFR 812.2 (c), a diagnostic device study is IDE exempt if the testing:
  - Is noninvasive
  - Does not require an invasive sampling procedure that presents a significant risk
  - Does not by design or intention introduce energy into a subject
  - Is not used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure

When is a Diagnostic Device Noninvasive?

- "A noninvasive device is one that does not, by design or intention:
  - penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra; or
  - enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os (21 CFR 812.3(k))."

http://tinyurl.com/hkjk3fp

How Do I Determine if an Invasive Sampling Procedure Presents a Significant Risk?

"…we recommend that you base your risk determination on the nature of the harm that may result from sampling. For example, FDA considers sampling techniques that require **biopsy of a major organ, use of general anesthesia, or placement of a blood access line into an artery or large vein** (subclavian, femoral, or iliac) to present a significant risk."

"Blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for noninvestigational purposes is also considered noninvasive (21 CFR 812.3(k))."

http://tinyurl.com/hkjk3fp

What Does Confirmation by another Medically Established Product Mean?

"…test results …should not influence patient treatment or clinical management decisions before the diagnosis is established by a medically established product or procedure"

"…If an investigational test uses a new technology or represents a significant technological advance, established diagnostic products or procedures may not be adequate to confirm the diagnosis provided by the investigational IVD."

http://tinyurl.com/hkjk3fp

Diagnostic Exemption Criteria

- Per 21 CFR 812.2 (c), a diagnostic device study is IDE exempt if the testing:
  - Is noninvasive
  - Does not require an invasive sampling procedure that presents a significant risk
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Clinical Investigation of a Medical Device

- Objective of the study is to assess the safety or effectiveness of the device

Be exempt of the IDE regulations
(21 CFR 812.2 (c))

Have an approved IDE
a) abbreviated IDE (21 CFR 812.2 (b)) b) IDE (21 CFR 812.20)

What is the difference between an abbreviated IDE and an IDE?

Who is overseeing the study:

IRB *(abbreviated IDE)*

- Non-significant risk (NSR) device studies

FDA and IRB *(IDE)*

- Significant risk (SR) device studies

Significant Risk Device Studies

- A **significant risk** device is one that:
  - Is intended as an implant and presents a potential for serious risk to the health, safety, and welfare of a subject.
  - Is used to support or sustain human life.
  - Is of substantial importance in diagnosing, curing, mitigating, or treating disease and/or otherwise preventing impairment of human health.
  - Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Note: The study risk determination is based on the proposed use of a device in an investigation, and not on the device alone.

Significant Risk (SR) Device Studies

Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors

Significant Risk and Nonsignificant Risk Medical Device Studies

http://tinyurl.com/48ywrw8

Study Risk Determination

Sponsor Risk Assessment

(based on clinical protocol, description of device, reports of prior investigations, subject selection criteria, etc.)

↓

Submit to IRB

NSR Agreement ↙

Requires an abbreviated IDE

Non-Significant Risk (NSR) Device Studies

- NSR device studies do not need an IDE application approved by FDA.
- The IRB serves as the FDA's surrogate for review, approval, and continuing review of NSR device studies.
- NSR device studies must follow the abbreviated requirements at 21 CFR 812.2 (b).

Abbreviated IDE Requirements
(21 CFR 812.2 (b)(1))

- Label the device properly (21 CFR 812.5)
- Obtain and maintain IRB approval after presenting why the device study is NSR
- Obtain informed consent (21 CFR 50)
- Monitor the study (21 CFR 812.46)
- Maintain required records and reports
- Comply with prohibitions against promotion (21 CFR 812.7)

Study Risk Determination

Sponsor Risk Assessment

(based on clinical protocol, description of device, reports of prior investigations, subject selection criteria, etc.)

↓

Submit to IRB

NSR Agreement

Requires an abbreviated IDE	Unsure of NSR/SR; Request FDA Input

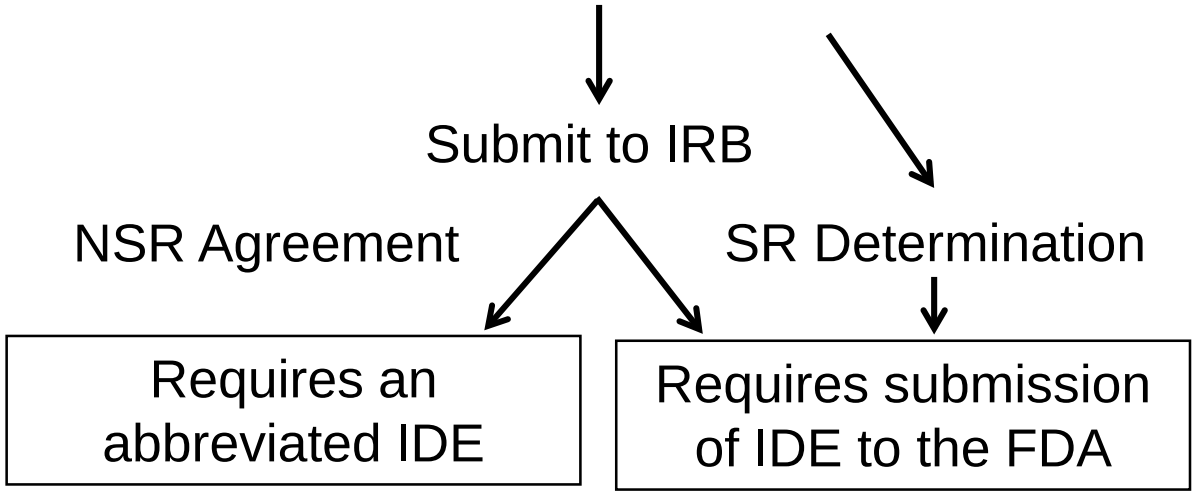
Study Risk Determination

- Q-Submission: Study Risk Determination Request
  - Include device information and clinical protocol
  - Include cover letter and highlight nature of request
  - Response usually within 60 days (binding determination)
- Full IDE Submission
  - Response within 30 days

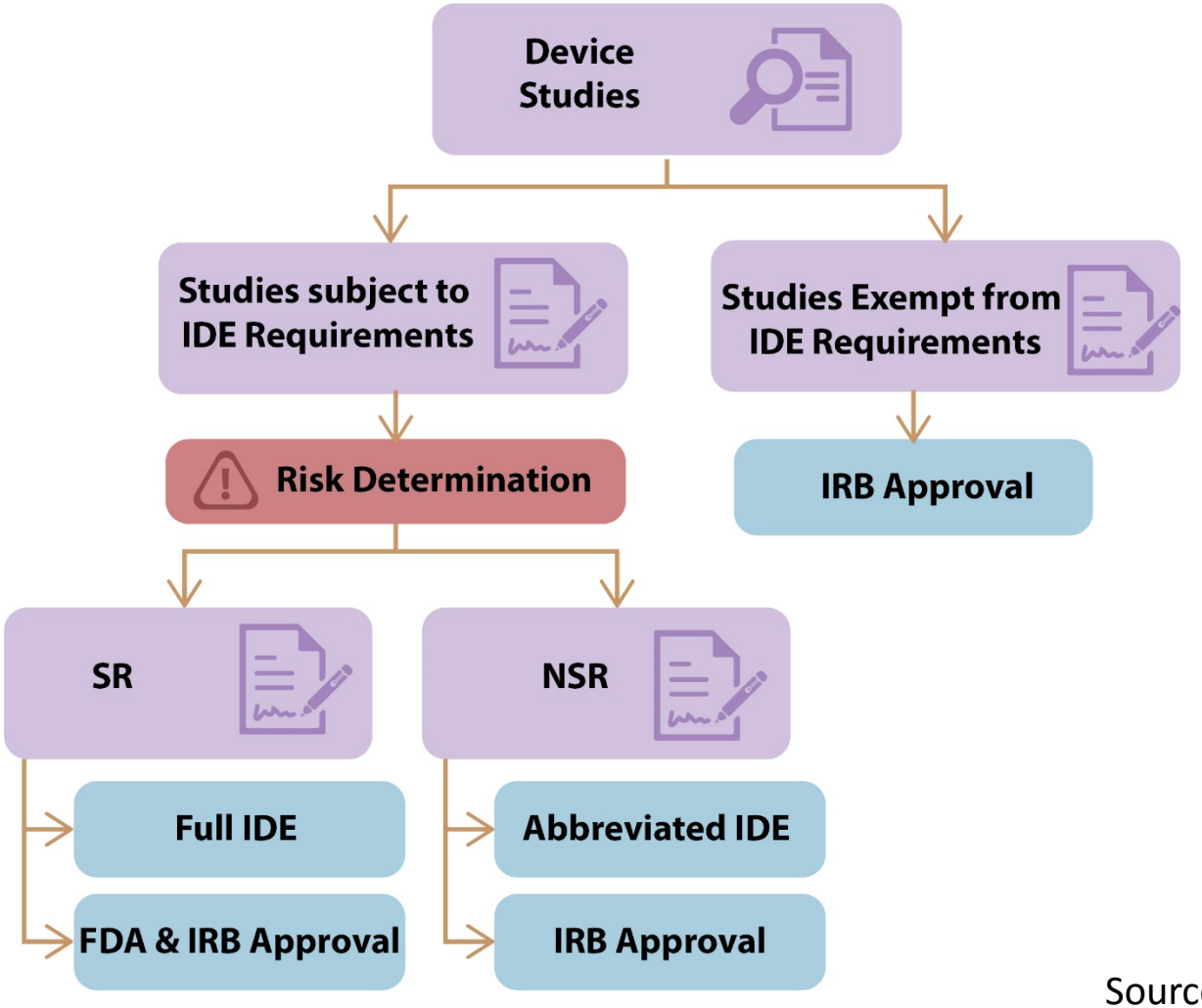
Study Risk Determination

Sponsor Risk Assessment

(based on clinical protocol, description of device, reports of prior investigations, subject selection criteria, etc.)



Clinical Investigation of a Medical Device



Source: ReGARDD

Let’s Practice…

Scenario 1

- **Contact lens solutions intended for use in lubricating/rewetting would be considered a:**

  a. device

  b. drug

  c. biologic

Scenario 2

- The objective of the study is to assess which of 2 FDA-approved imaging devices provides better images for diagnosis and evaluation of stroke.
- The devices used in the study are: 3D Volumetrics scanner and Siemens Antares scanner and appear to be used per their approved label.

Scenario 3

- An investigator is evaluating the utility of a software program for motion correction in MRI imaging.
- The MRI pulse sequences used to perform these scans are FDA approved.
- Images collected as part of routine clinical care will be analyzed using this software and compared to those processed conventionally.

Scenario 4

- An investigator is assessing whether there is a correlation between circulating tumor DNA (ctDNA) levels before chemotherapy treatment and disease-free and overall survival in breast cancer patients.
- If a correlation exists, this information could be used in the future to determine who would most benefit from chemotherapy treatment.
- The investigator will collect blood samples before chemotherapy treatment, quantitate ctDNA levels using an assay developed in her lab, and continue to follow the patients to collect survival endpoint data.

Let’s Take a Break!

The plan to increase productivity by canceling coffee breaks flopped.

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PART 2: IDE Best Practices and Additional Studies

- IDE Preparation and Submission
- IDE Maintenance
- Expanded Access Program
- Algorithms and Mobile Medical Applications

IDE Content (21 CFR 812.20 (b))

Cover Sheet – Form FDA 3514

1. Name and Address of the Sponsor
2. Report of Prior Investigations
3. Investigational Plan
4. Manufacturing Information
5. Investigator Agreement
6. Investigator Certification
7. IRB Information
8. Name and Address of Investigators Institution
9. Financial Claims
10. Environmental Assessment
11. Labeling
12. Informed Consent
13. Additional Information

Cover Sheet – Form FDA 3514

- Used voluntarily
- Same form is used for IDE, 510(k), PMA, meetings, 513(g), etc.
- Captures the following information:
  - original submission, amendment, report or supplement
  - device information (name, intended use, classification)
  - sponsor and manufacturer contact information
  - any previous discussion with the FDA

IDE Content

21 CFR 812.20 (b)

Cover Sheet – Form FDA 3514

1. Name and Address of the Sponsor
2. Report of Prior Investigations

2. Report of Prior Investigations
(21 CFR 812.27)

- The report of prior investigations shall include reports of all prior clinical, animal, and laboratory testing of the device and shall be comprehensive and adequate to justify the proposed investigation.
- Specific Contents:
  - Bibliography of all publications
  - Summary of all unpublished information
  - If nonclinical laboratory studies are referenced, state whether studies were conducted in accordance with good laboratory practice (GLP) regulations (21 CFR 58)

IDE Content

21 CFR 812.20 (b)

Cover Sheet – Form FDA 3514

1. Name and Address of the Sponsor
2. Report of Prior Investigations
3. Investigational Plan

3. Investigational Plan

(21 CFR 812.25)

- Purpose
  - Name and intended use of the device
  - Objectives and duration of the investigation
- Protocol
  - Methodology
- Risk Analysis
- Description of the Device
- Monitoring Procedures
- Additional Records and Reports

IDE Content

21 CFR 812.20 (b)

Cover Sheet – Form FDA 3514

1. Name and Address of the Sponsor
2. Report of Prior Investigations
3. Investigational Plan
4. Manufacturing Information

4. Manufacturing Information

21 CFR 812.20(b)(3)

- FDA-Approved Device – off label and/or modified
  - Refer to the approved product label & describe any changes
- Non-FDA Approved Device – from a company
  - Include manufacturing information provided by the company
  - Refer to a Letter of Authorization (LoA)
- Non-FDA Approved Device – you control manufacturing
  - Methods, facilities, and controls for manufacturing, packaging, storage and installation of the device

What is an LoA?

- This is a letter from a sponsor (company) to their IDE (or IND or MF) stating that confidential information from their submission can be used in support of your submission.
- It gives the FDA “permission” to reference the named materials in support of your IDE application.
- Get copies of the letters to include in your submission!

IDE Content

21 CFR 812.20 (b)

Cover Sheet – Form FDA 3514

1. Name and Address of the Sponsor
2. Report of Prior Investigations
3. Investigational Plan
4. Manufacturing Information
5. Investigator Agreement

5. Investigator Agreement
(21 CFR 812.43)

- **Who is the investigator?**
  - The investigator is the individual who actually conducts a clinical investigation (i.e., under whose immediate direction the investigational device is administered, dispensed to, or used involving human subjects).
  - In the event of an investigation being conducted by a team of individuals, "investigator" refers to the responsible leader of that team.

5. Investigator Agreement
(21 CFR 812.43)

- CV of the investigator
- Statement of investigator's relevant experience
- If the investigator was involved in an investigation that was terminated, explain the circumstances
- Financial disclosure information
- Statement of investigators commitment to:
  - Conduct the investigation according to the agreement
  - Supervise all testing
  - Ensure that requirements for obtaining IC are met

IDE Content (21 CFR 812.20 (b))

Cover Sheet – Form FDA 3514

1. Name and Address of the Sponsor
2. Report of Prior Investigations
3. Investigational Plan
4. Manufacturing Information
5. Investigator Agreement
6. Investigator Certification
7. IRB Information
8. Name and Address of Investigators Institution
9. Financial Claims
10. Environmental Assessment
11. Labeling
12. Informed Consent
13. Additional Information

Original IDE Submission

- 3 copies of your application are required:
  - 1 Paper copy
  - 2 eCopies with a paper cover letter

Products regulated by CDRH:	Products regulated by CBER:
U.S. Food and Drug Administration **Center for Devices and Radiological Health** **Document Control Center- W066-G609** **10903 New Hampshire Avenue** **Silver Spring, MD 20993-0002**	**U.S. Food and Drug Administration** **Center for Biologics Evaluation and Research** **Document Control Center** **10903 New Hampshire Avenue** **WO71, G112** **Silver Spring, MD 20993-0002**

eCopy Requirements

- eCopy should be an exact duplicate of the paper copy
  - If an identical copy is not feasible, the paper copy must have a placeholder cross-referencing the location of information on the eCopy
  - Cover letter must contain a valid eCopy statement
  - Sent on electronic media (CD, DVD, or flash drive)
  - All documents need to be in Portable Document Format (PDF) with no security settings
  - Use Adobe Acrobat 11 and below
  - 50MB or smaller in size

Creating an eCopy

- Non-Volume Based eCopy
  - 001_G010101_Progress Report 2017.pdf
- Volume Based eCopy
  - VOL_001_Aministrative Information
  - VOL_002_Report of Prior Investigations
    - 001_Clinical.pdf
    - 002_Animal Testing.pdf

http://tinyurl.com/99jtgle

Ensure eCopy Compliance

- eSubmitter-eCopies Tool: a voluntary tool that formats your eCopy content and allows you to download onto a local drive
- eCopies Validation Module: a voluntary tool that verifies the format of an eCopy you have already developed on your local drive

FDA Review Process

- **Sponsors are notified of the date that FDA receives the original application.**
- **IDE number is assigned** (e.g., G096000)
  - If eCopy is missing, you will be placed on "eCopy Hold"
    - ✓ To lift the hold, send revised eCopy only, with a paper cover letter and an appropriate eCopy statement

FDA Review Process

- **Within 30 calendar days of the receipt date, FDA may grant:**
  - IDE Approval
  - IDE Approval with Conditions
  - Staged Approval (with Conditions)
  - IDE Disapproval
- **An IDE application is considered approved 30 days after it has been received by FDA.**

http://tinyurl.com/lxrmd9u

PART 2: IDE Best Practices and Additional Studies

- IDE Preparation and Submission
- IDE Maintenance
- Expanded Access Program
- Algorithms and Mobile Medical Applications

Once you have an active IDE…

- Make sure that you also have IRB approval(s) in place
- Register trial at the ClinicalTrials.gov

ClinicalTrials.gov

- Introduced by FDAAA in 2007
- Do not need to send a 3674 form to the FDA with your IDE submission
- Do need to register “applicable clinical trial” on ClinicalTrials.gov
  - Other reasons to register: publishing, NIH funding

Requirements for IDE Modifications

- Modifications to the Investigational Plan (device or clinical protocol) need to be submitted to FDA:
  - Changes that REQUIRE prior approval (30-day reply from FDA)
  - Changes that DO NOT require prior approval (5-day notice)
  - Changes submitted as a part of annual report

http://tinyurl.com/42wvtny

IDE Modifications

- Changes that require prior approval (30-day reply from FDA):

  Changes that could impact validity of data, scientific soundness, or the rights/safety/welfare of study subjects:

Indication	**Type or nature of study control**	**Primary end point**
Significant design changes	**Statistical methods evaluation**	**Expanding the study**

IDE Modifications

- Changes that require 5-day notice to FDA:
  - Emergency change
  - Changes that do not affect validity of data, scientific soundness, or the rights/safety/welfare of study subjects:

Modification of inclusion/exclusion criteria	**Increasing frequency at which information is gathered**
Design or manufacturing changes that are not significant	**Modifying the secondary study endpoints**

IDE Modifications

- Changes that can be sent to FDA as part of the annual report:
  - Minor changes that do not affect the validity of data, scientific soundness, or the rights/safety/welfare of study subjects:

Monitoring procedures	**Labeling**	**Informed Consent Materials**
IRB Information	**Purpose of the study**	**Risk Analysis**

IDE Maintenance

IDE Report	Timeline
Unanticipated Adverse Device Effects	10 working days
Withdrawal of IRB approval	5 working days
Investigator List	Every 6 months
Progress Report (Annual Report)	At least yearly
Deviation from Investigational Plan	5 working days or pre-approval
Failure to Obtain Informed Consent	5 working days
Recall and Device Disposition	30 working days
Significant Risk Determination	5 working days
Final Report	30 working days- notification 6 months- report

IDE Maintenance - UADEs

- Unanticipated Adverse Device Effect - 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 (21 CFR 812.3 (s))
- Conduct an evaluation of the UADE and report to the FDA within 10 working days

Progress/Final Report

1. Basic information
2. Study Progress
   - Brief summary of the study progress
   - Number of investigators/investigational sites
   - Number of subjects enrolled
   - Number of devices shipped
   - Disposition of all device shipped
   - Brief summary of results
   - Summary of anticipated and unanticipated adverse effects
   - Description of any deviations from the investigational plan (since last progress report)

Progress/Final Report

3. Risk Analysis
   - Summary of any new adverse information (since the last progress report) that may affect the risk analysis
   - Reprints of any articles published from data collected from this study
   - New risk analysis, if necessary, based on new information and on study progress
4. Other Changes
   - Summary of any changes in manufacturing practices and quality control
   - Summary of all changes in the investigational plan not required to be submitted in a supplemental application
5. Marketing Application or Future Plans

IDE Submission Types

- Supplements
- Reports
- Amendments

http://tinyurl.com/lxrmd9u

Supplements

- Approval for change (prior-approval, 5-day notice)
- Request approval for a new study under the same IDE
- Request study expansion (new sites, more patients)
- Request approval to terminate enrollment/study
- Notify FDA if the study been suspended
- Request approval for the compassionate use
- Request the extension of time to respond to the FDA

The FDA will usually reply to supplements. Reply is similar to the Original IDE submission.

Reports

- Provide biannual investigator/IRB information
- Annual reports
- Failure to obtain ICF
- Notify the FDA of the Emergency Use
- Report the unanticipated adverse device effect
- Report completion of enrollment/study
- Provide final IDE report

The FDA will reply within 30 days <u>only</u> if they have any comments or questions.

Amendments

- Any repose to deficiency letter is an amendment.
  - Response to Disapproval
  - Response to Approval with Conditions
  - Response to Refuse to Accept
  - Response to Report Deficient
  - Voluntary Withdrawal by Sponsor

An amendment may be submitted to each of the 3 parent document types: Original IDE submission, IDE Supplement, or an IDE Report.

Terminating/Closing an IDE

- If IDE is not yet approved: request a withdrawal
- If you have an active IDE, but no subjects enrolled: request a withdrawal, but state why and account for all the device
- If subjects have been enrolled: you might need to complete follow-up of already enrolled subjects
- If you completed the study: notify FDA within 30-days and send Final Report within 6 months

PART 2: IDE Best Practices and Additional Studies

- IDE Preparation and Submission
- IDE Maintenance
- Expanded Access Program
- Algorithms and Mobile Medical Applications

Expanded Access

- **Emergency Use of Unapproved Medical Device**
  - The patient has a life-threatening or serious disease or condition that needs immediate treatment;
  - No generally acceptable alternative treatment for the condition exists; and
  - Because of the immediate need to use the device, there is no time to use existing procedures to obtain FDA approval for the use.

Expanded Access

- **Emergency Use-** An unapproved medical device may be used in an emergency situation without prior FDA approval provided that the physician obtains:
  1. Informed consent from the patient or a legal representative;
  2. Clearance from the institution as specified by their policies;
  3. Concurrence of the IRB chairperson;
  4. An independent assessment from an uninvolved physician; and
  5. Authorization from the device manufacturer.

- Must notify FDA of the emergency use within 5 days

Expanded Access

- **Compassionate Use IDE** (Individual Patient/Small Group Access):
  - Life-threatening or serious condition
  - No generally acceptable alternative treatment exists
  - Prior approval of FDA and IRB is required
  - Time-frame: during clinical trial

- **Treatment Use IDE**:
  - Life-threatening or serious condition
  - No generally acceptable alternative treatment exists
  - Device is under investigation for the same use under an approved IDE or all clinical trials have been completed
  - Sponsor is pursuing marketing approval/clearance of the investigational device with due diligence
  - Prior approval of FDA and IRB is required
  - Time-frame: late stage clinical trials or after trial completion

Additional Types of Device Studies

- **Humanitarian Device Exemption (21 CFR 814.100)**
  - An Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 8,000 individuals in the US per year
  - HDE application is similar to PMA but is exempt from the effectiveness requirements.
  - With exception of emergency use, even if used per its approved label, the use of HUD requires IRB approval

PART 2: IDE Best Practices and Additional Studies

- IDE Preparation and Submission
- IDE Maintenance
- Expanded Access Program
- Algorithms and Mobile Medical Applications

Algorithms

- An algorithm is a device that:
  - combines multiple variables using an interpretation function to yield a single, patient-specific result that is intended for use in the diagnosis of a disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, and
  - the result is non-transparent and cannot be independently derived or verified by the end user.

- Examples:
  - A device that integrates quantitative results from multiple immunoassays to obtain a qualitative “score” that predicts a person’s risk of developing a disease or condition.
  - A device that integrates a patient’s age, sex, and genotype of multiple genes to predict risk of or diagnose a disease or condition.

Algorithm as a Medical Device

- Any calculation that would have a multiple inputs and would result in an output that will be used to assign a patient to a specific treatment regimen would be considered an algorithm.
- All algorithms are subject to 21 CFR 812, regardless of format.
- Even if the study is designed in a way that the “calculation” randomizes the patients to the drug/device whose label is so broad that the treatment itself is “within the label”, the calculation/formula based on which the treatment is assigned would still be considered an algorithm.

Regulation of Algorithms

- Device classification is based on the intended use and level of controls necessary to assure safety and effectiveness.

  Example: A device intended as an indicator of a patient's risk of cancer recurrence may be a Class II device, while the same device intended to predict which patients should receive chemotherapy might be a Class III device.

  - In a clinical study, this could be the difference between NSR and SR determinations.

Mobile Medical Applications

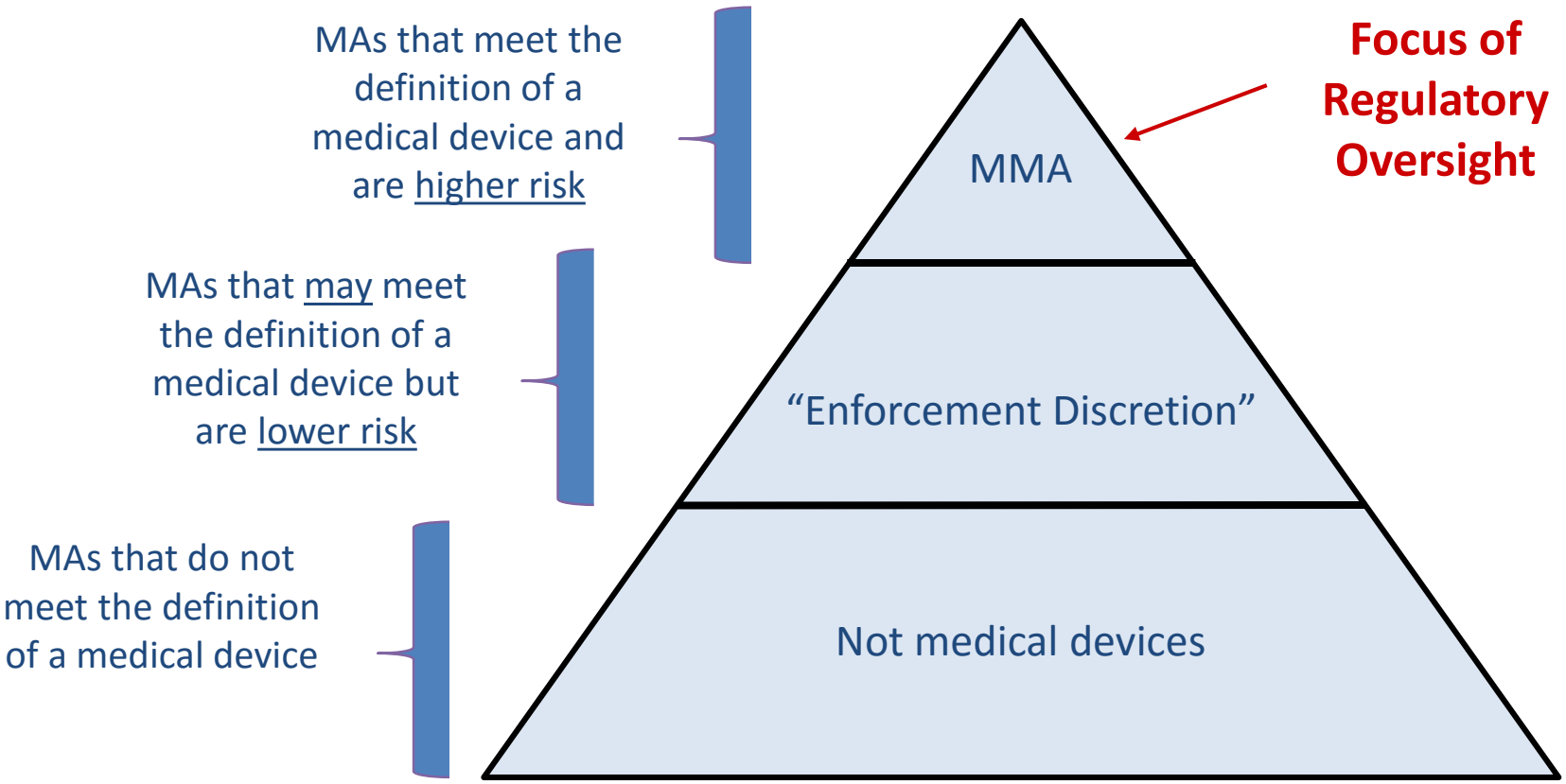
Mobile Application (Mobile App)

- ". . .defined as a software application that can be executed (run) on a mobile platform. . ., or a web-based software application that is tailored to a mobile platform but is executed on a server."

Mobile Medical Application (MMA)

- ". . .is a mobile app that meets the definition of device in section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); **and** either is intended:
  - ✓ *to be used as an accessory to a regulated medical device; or*
  - ✓ *to transform a mobile platform into a regulated medical device."*

Risk-based Approach for Mobile Applications



Mobile Apps that are NOT Medical Devices

Mobile Apps that could be used in a healthcare environment, in clinical care or patient management, but are **NOT** considered medical devices:

1. *Mobile apps that are intended to provide access to electronic "copies" (e.g., e-books, audio books) of medical textbooks or other reference materials.*
2. *Mobile apps that are intended for health care providers to use as educational tools for medical training.*
3. *Mobile apps that are intended for general patient education and facilitate patient access to commonly used reference information.*
4. *Mobile apps that automate general office operations in a health care setting.*
5. *Mobile apps that are generic aids or general purpose products.*

Mobile Medical Apps: Focus of FDA Regulatory Oversight

Mobile Apps that meet the definition of a medical device and can pose potential risk to public health:

1. Mobile apps that are an extension of one or more medical devices by connecting to such device(s) for purposes of controlling the device(s) or for use in active patient monitoring or analyzing medical device data.
2. Mobile apps that transform the mobile platform into a regulated medical device by using attachments, display screens, or sensors or by including functionalities similar to those of currently regulated medical devices.
3. Mobile apps that become a regulated medical device (software) by performing patient-specific analysis and providing patient-specific diagnosis, or treatment recommendations.

Enforcement Discretion

Mobile Apps that may meet the definition of a medical device for which the FDA intends to exercise 'enforcement discretion':

- Mobile apps for providers that help track or manage patient immunizations by assessing the need for immunization, consent form, and immunization lot number
- Help patients document, show, or communicate potential medical conditions to health care providers.
- Guide a user through a questionnaire of signs and symptoms to provide a recommendation for the type of health care facility most appropriate to their needs

21st Century Cures Act

Removed some low risk software products from FDA oversight.

- Software for administrative support of healthcare facilities
- “Healthy lifestyle” software that provides no diagnostic, prevention or treatment function
- Electronic patient records
- Medical Device Data Systems- Software for transferring, storing or displaying medical device or clinical laboratory test data but that does not support interpretation or analyze clinical data
- Clinical Decision Support Software- Software to display, analyze, or print medical information for supporting or providing recommendations to healthcare providers

Let’s Practice…

Discussion Question 1

An investigator is running a multi-center trial. In 3 out of 4 participating institutions, the reviewing IRBs agreed with the investigator that the device trial is a NSR study. The 4th IRB sees it as SR device study.

What should the investigator do?

a) ignore the 4th IRB, since 3 others agreed
b) do not use the 4th site
c) Alert the FDA of the SR determination within 5 days

Discussion Question 2

All of the following IDE reports are required to be submitted to the FDA within **5 working days** except:

a) Withdrawal of IRB Approval
b) Unanticipated Adverse Device Effect
c) Deviation from the Investigational Plan
d) Failure to Obtain Informed Consent

Discussion Question 3

A sponsor-investigator is developing a novel device to enable ablation of epileptic loci in the brain by a surgical robot. The sponsor-investigator has completed an early feasibility study in 5 patients with promising results and would like to perform a larger feasibility study evaluating safety and efficacy endpoints in more subjects. The submission of this new clinical study protocol is best submitted as:

a) An Original IDE Application
b) A Report to the Existing IDE
c) A Supplement to the Existing IDE
d) An Amendment to the Existing IDE

Mobile Medical Applications

For each of the following descriptions, please determine whether the mobile application is:

- ❑ Regulated MMA
- ❑ Enforcement Discretion
- ❑ Not a medical device

Scenario 1

- Mobile apps that use GPS location information to alert asthmatics of environmental conditions that may cause asthma symptoms.
  - Regulated MMA
  - Enforcement Discretion
  - Not a medical device

Scenario 2

- A mobile app which is a game that simulates various cardiac arrest scenarios to train health professionals in advanced CPR skills.
  - ❑ Regulated MMA
  - ❑ Enforcement Discretion
  - ❑ Not a medical device

Scenario 3

- A mobile app which uses a electrodes and sensors attached to the mobile platform to measure physiological parameters during CPR and provides feedback about the quality of CPR being delivered.
  - Regulated MMA
  - Enforcement Discretion
  - Not a medical device

Scenario 4

- Mobile apps that use video and video games to motivate patients to do their physical therapy exercises at home.
  - Regulated MMA
  - Enforcement Discretion
  - Not a medical device

Useful Websites:

CDRH Learn Course List

http://www.fda.gov/Training/CDRHLearn/default.htm

Device Advice:

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm

Thank you!

Questions?
Please contact us at
ORAQ@dm.duke.edu