

Clinical Trials and Investigational Device Exemptions

**FDA Small Business
Regulatory Education for Industry (REdI)
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Learning Objectives

- To understand the regulatory context of device clinical investigations
- To understand when an IDE is required
- To understand the IDE application process and FDA decisions on those applications
- To understand ways to have more successful IDE submissions

Poll Question

D1S4-1

View Votes

Edit

End Poll

Have you ever submitted an IDE to FDA?

<input type="radio"/> Yes	<div></div>	0%	(0)
<input type="radio"/> No	<div></div>	0%	(0)
<input checked="" type="radio"/> No Vote			

☒ Broadcast Results

Poll Question

D1S4-2

View Votes

Edit

End Poll

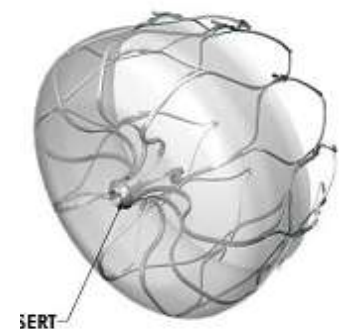
Do you plan to conduct a clinical trial for a device in the next 2 years?

<input type="radio"/> Yes	<div></div>	0%	(0)
<input type="radio"/> No	<div></div>	0%	(0)
<input type="radio"/> Maybe	<div></div>	0%	(0)
<input checked="" type="radio"/> No Vote			

☒ Broadcast Results



“Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world.”



CDRH Vision Statement

Innovation *and* Protection



Investigational Device Exemptions

*The purpose of this part is to encourage, to the extent consistent with the **protection of public health and safety**, ... the **discovery and development of useful devices** intended for human use....*

21 CFR 812.1

Overview

- What is an IDE and when is one needed?
- The IDE application and beyond
- Tips for successful IDE submissions

Overview

- **What is an IDE and when is one needed?**
- The IDE application and beyond
- Tips for successful IDE submissions

Investigational Device Exemption

- 21 CFR 812.1:

*“...An approved **investigational device exemption (IDE)** permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be **shipped lawfully** for the purpose of **conducting investigations** of that device....”*

- An IDE is a **regulatory submission** that permits clinical investigation of devices.

Approved IDEs are Exempt from Regulations Pertaining to:

- Misbranding
- Registration
- Performance Standards
- 510(k)
- PMA
- HDE
- Good Manufacturing Practices (GMPs) **except Design Controls**
- Color Additive requirements
- Banned Devices
- Restricted Device requirements

Some Terminology

- **Investigation:** clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device (also study)
- **Sponsor:** initiates, but does not actually conduct, the investigation
- **Investigator:** actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject
- **Institutional Review Board (IRB):** reviews, approves (initially and continuing) biomedical research at a given institution

Provisions of the IDE Regulation

- Describes **applicability** of the IDE regulations
- Provides **administrative** information
- Outlines the contents of the **IDE application**
- Describes **FDA actions** on IDE applications
- Assigns **responsibilities** to all participants in clinical investigation

Studies Subject to the Regulation

- To gain initial safety and effectiveness information to support further study
- To support marketing application [PMA, HDE, 510(k) or *de novo*]
 - New device
 - New use of legally marketed device (“off-label use”)
- Sponsor-investigator studies of unapproved devices or new intended use of approved device (even if no marketing application planned)

Types of device studies

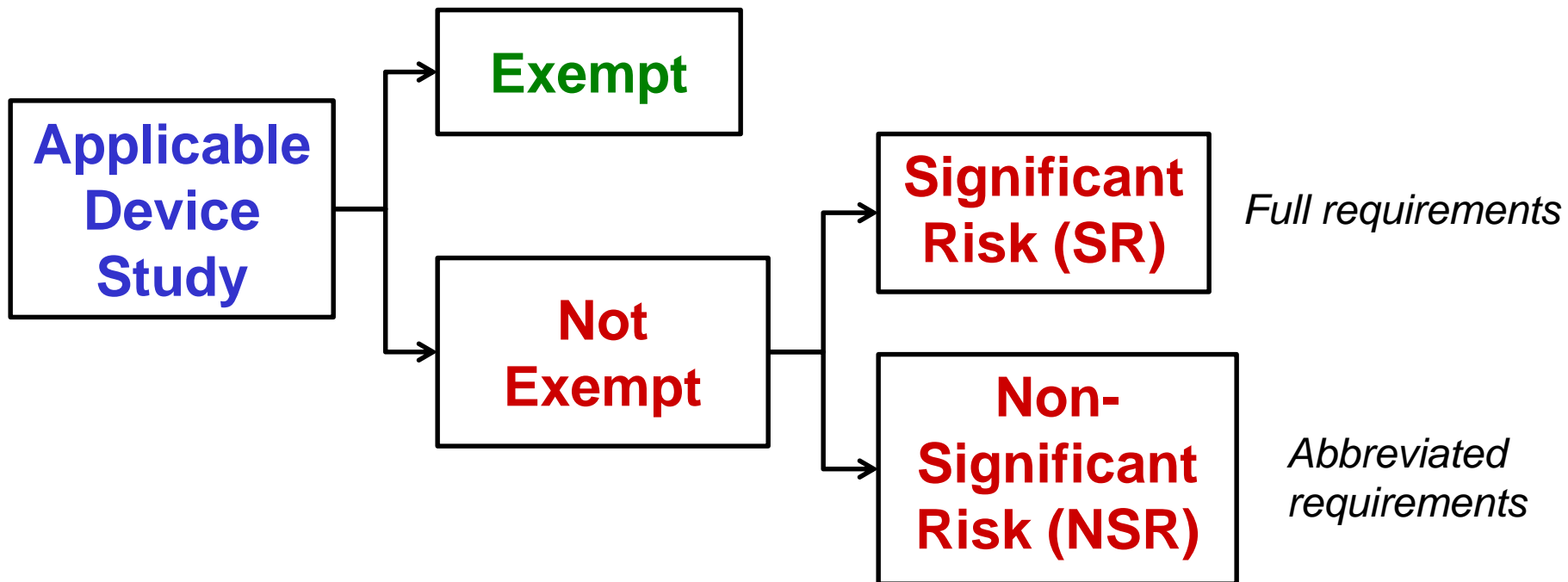
- **Feasibility Studies**

- Intended to gather preliminary information regarding
 - Safety profile and potential for effectiveness
 - Refinements to device or future study
- Not intended to provide primary support for marketing
- Generally not statistically driven ($n \approx 1-40$ subjects)
- Early feasibility studies to inform device design

- **Pivotal Studies**

- Intended to provide the primary clinical data in support of a future marketing application
- Statistically driven sample size and hypotheses

When is an IDE needed?



Is it an “applicable” device study?

General applicability of the IDE regulations:

812.2(a) General. This part applies to all clinical investigations of devices to **determine safety and effectiveness**, except as provided in paragraph (c) of this section.

Device studies where **safety/effectiveness** of the devices is not being evaluated are not subject to the IDE regulations.

Basic Physiological Research

- Investigating a physiological principle
- Only using the device to address the research question
- Not evaluating device **safety/effectiveness**
- Outside of the scope of the IDE regulations – No IDE required

“Practice of Medicine”

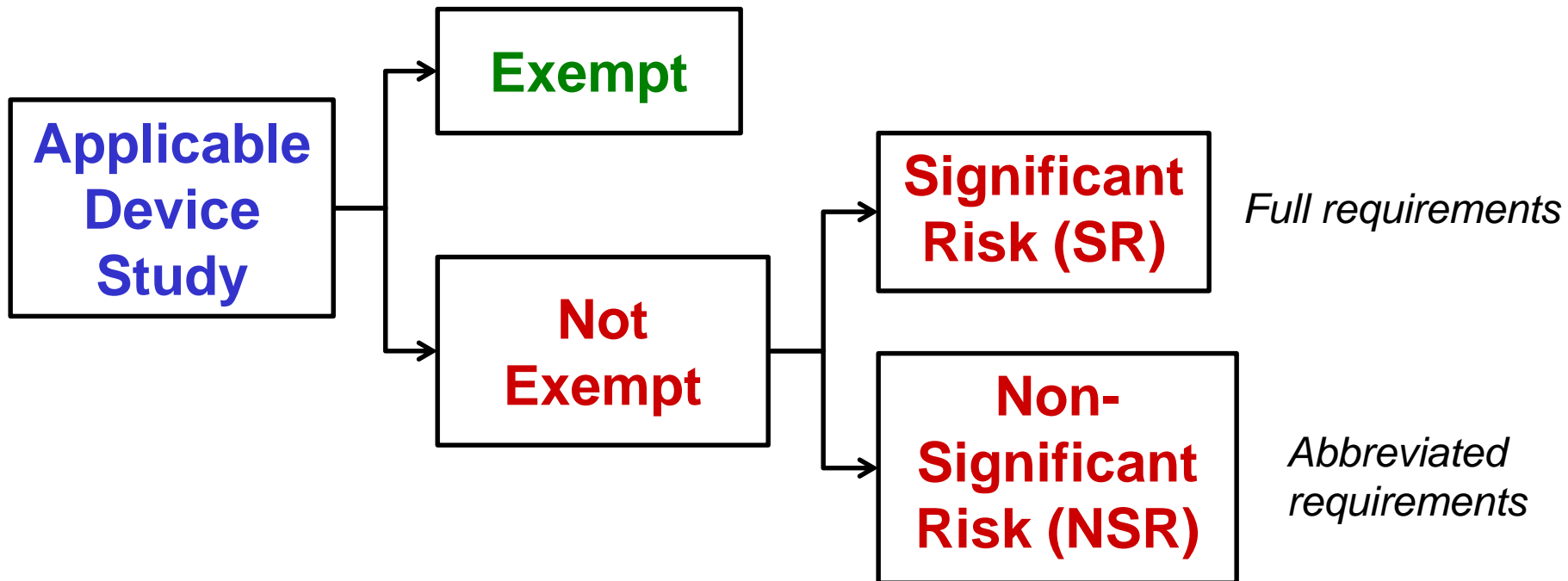
“Nothing in this Act shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship....”

From Section 1006 of the FD&C Act

“Practice of Medicine”

- Not an investigation/study
- Physician should:
 - Be well informed about the product
 - Use firm scientific rationale and sound medical evidence
 - Maintain records on use and effects
- **IDE not required**; institution may require IRB review/approval and informed consent
- Other prohibitions still apply

When is an IDE needed?

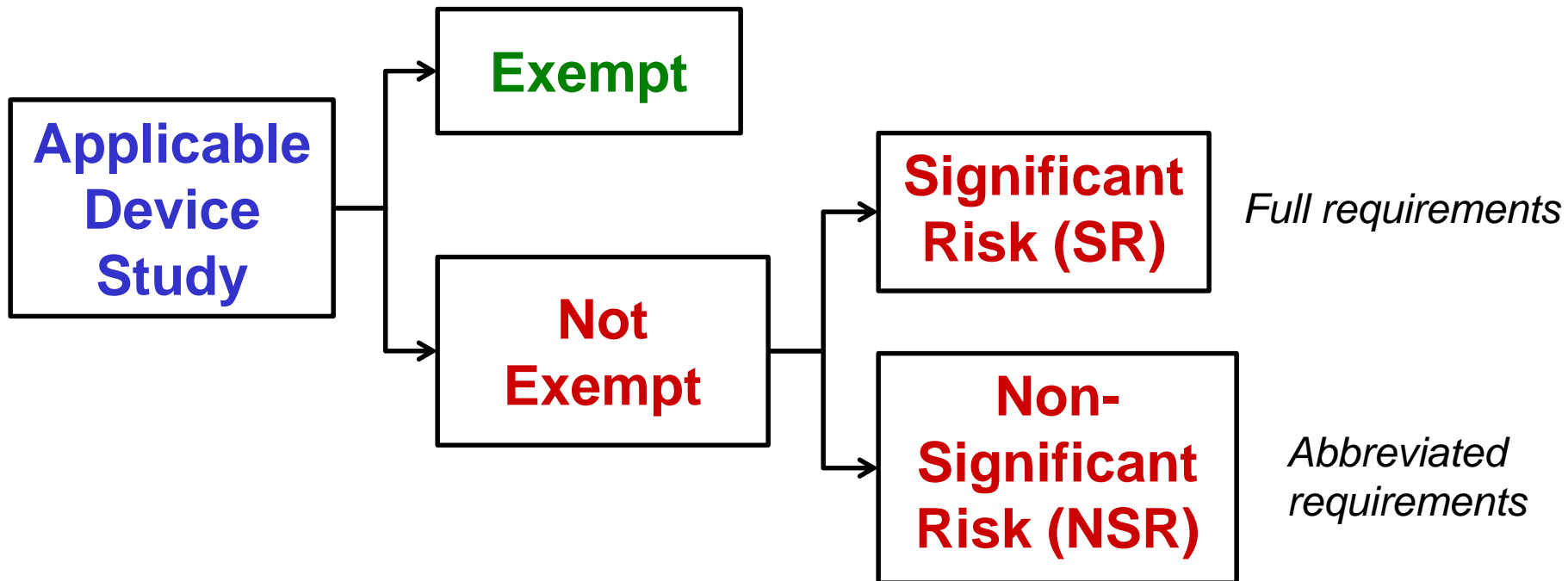


Exempt Studies (21 CFR 812.2(c))

No IDE Needed

- Commercial devices used in accordance with labeling
- Many diagnostic devices
- Testing of consumer preference, of a modification, or of a combination of devices
 - if not for the purpose of determining safety or effectiveness and not putting subjects at risk:
- Veterinary devices
- Research on/with laboratory animals
- Custom devices as defined in 812.3(b)

When is an IDE needed?



Significant Risk (SR) Study

- A significant risk ***device*** presents a **potential for serious risk to the health, safety, and welfare of a subject** and is:
 - An implant; or
 - Used in supporting or sustaining human life; or
 - Of substantial importance in diagnosing, curing, mitigating, or treating disease or preventing impairment of human health; or
 - Otherwise poses a risk

812.3(m)

- ***Study*** risk based on the **proposed use** of a device in an investigation, **NOT** the **device alone**

Non-Exempt Studies

- **Non-Significant Risk** – does not require IDE submission to FDA
 - abbreviated requirements
 - Labeling (812.5)
 - IRB Approval (56)
 - Informed Consent (50)
 - Monitoring (812.46)
 - Records and Reports (812.140(b)(4) and (5), 812.150(b)(1) - (3) and (5) - (10))
 - Annual and Final Progress Reports are not required
 - Promotion (812.7)
- **Significant Risk** – can not begin until FDA approves IDE (full requirements)

Non-Significant Risk (NSR) Studies

- IRB serves as the FDA's surrogate for review, approval, and continuing review of the NSR device studies.
- A NSR device study may start at the institution as soon as the IRB reviews and approves the study
 - Abbreviated IDE requirements (labeling, IRB, consent, monitoring, reporting, prohibition on promotion)
 - No IDE submission to FDA needed

Significant Risk Studies

- Full IDE requirements apply
- Sponsor submits IDE application to FDA
- FDA renders decision within 30 calendar days
- If approved, sponsor obtains IRB approval
- After both FDA and IRB approve the investigation, study may begin

Study Risk Determination Inquiries to FDA

- Sponsor submits “Study Risk Determination” Q-Submission
 - Cover letter, Device Description, Protocol
- FDA issues letter indicating if study is
 - Basic physiological research
 - Exempt
 - Not exempt: SR or NSR
- FDA is final arbiter

Resources:

[Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with FDA Staff](#)

[Significant Risk and Nonsignificant Risk Medical Device Studies](#)

Overview

- What is an IDE and when is one needed?
- **The IDE application and beyond**
- Tips for successful IDE submissions

The IDE Application (21 CFR 812.20)

- Name and address of sponsor
- Report of prior investigations and investigational plan
- Manufacturing, processing, packing, and storage of device
- Investigator agreement (example, listing, certification)
- List of the name, address, and chairperson of each IRB
- Participating institutions
- Amount to be charged for device
- Environmental assessment
- Labeling
- Subject materials including informed consent
- Additional information requested by FDA

Investigational Plan (812.25)

Includes:

- Purpose of study
- Study protocol
- Risk analysis
- Device description
- Monitoring procedures
- Labeling, consent materials, IRB and institutional information
- Records and reports

FDA Review of the Application

- FDA sends acknowledgement with IDE number: GYYxxxx (e.g. G160001)
- IDE sent to appropriate review division based on intended use
- Lead reviewer assembles team of experts to review the application and make decision with management concurrence within 30 days
- FDA issues a decision letter to the sponsor

FDA Decisions and Letters

- **Approval**
 - Approves the trial for specified number of sites and subjects
 - Enrollment can begin once IRB approval is obtained
- **Approval with conditions**
 - Approves the trial for specified number of sites and subjects provided conditions (deficiencies) are addressed within 45 days
 - Enrollment can begin once IRB approval is obtained
- **Disapproval**
 - Study may not begin
 - Deficiencies will be listed
 - Sponsor must address deficiencies and obtain FDA approval to start study

FDA Review of Feasibility IDEs

- Focused on safety
- Critical issues
 - Reasonable study conceptually?
 - Adequate preclinical validation of device?
 - Why is clinical really the next necessary step?
 - Appropriate mitigation of potential risks?
 - Appropriate enrollment criteria?
 - Patients adequately informed?
 - Sample size appropriate?

FDA Review of Pivotal IDEs

- Focused on safety and plan for collecting and evaluating study data
- Additional critical issues
 - Trial endpoints
 - Randomization, blinding, follow-up, etc.
 - Study conduct and monitoring
 - Statistical analysis plan

IDE decision making

IDE **Disapproval** is appropriate when:

- Probable risks to the subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained
- Study does not pose a reasonable scientific question and/or is not designed to collect data related to that scientific question
- IDE does not comply with regulations, omits material or contains untrue statements

IDE decision making

- Concerns regarding the **study design** that **are not related to protecting study subjects** are not the basis for a disapproval
 - FDA will convey these concerns to the sponsor for their consideration as an attachment to our decision letter

Other Elements of FDA Letters

Study Design Considerations




- Recommendations regarding study design (unrelated to subject protection), for example:
 - Primary and important secondary endpoints and study success criteria
 - Randomization and control plan
 - Blinding (masking)
 - Follow-up duration and assessments
 - Statistical plan
 - Case report forms
 - Enrollment criteria
 - Core labs and independent adjudication committees

Other Elements of FDA Letters

Future Considerations

- Issues relevant for future submissions, for example:
 - Testing needed for future marketing application
 - Recommendations for future pivotal study design
 - Limitations on future claims based on study design

Summary: FDA Letter

- Decisions – Can you start the study?
 -  Approval
 -  Approval with Conditions
 -  Disapproval
- } Require deficiencies to be addressed
- Study Design Considerations and Future Considerations do NOT require a response.
 - “*FDA Decisions for Investigational Device Exemption (IDE) Clinical Investigations*”

Sponsor Responsibilities

- Select qualified **investigators** and provide them with information they need
- Ensure proper **monitoring**
- Obtain **IRB and FDA** review and approval
- Control **devices**
- **Comply** with labeling, prohibition of promotion, import and export requirements (Subpart A).
- Maintain adequate **records**
- Grant **inspections** to FDA (establishments and records)
- Prepare and submit **reports**

Other FDA Submissions

- **Supplements** (812.35)
 - Change in protocol
 - Change in device
- **Reports** (812.150)
 - Annual progress
 - Unanticipated adverse device effects
 - Enrollment and follow-up completion
 - Withdrawal of IRB or FDA approval
 - Current list of investigators
 - Final report
- Responses to any deficiencies are submitted as **amendments**
- All Original IDEs, Reports, Supplements, and their amendments have a 30-day review clock

Overview

- What is an IDE and when is one needed?
- The IDE application and beyond
- **Tips for successful IDE submissions**

Tips for Successful IDE Submissions

- **Before Submission**

- Q-submission Program
 - Study Risk Determination
 - Informational Meeting
 - No expectation of feedback
 - Pre-Submission
 - Request for feedback from FDA in the form of a written response or meeting on specific questions
- Review relevant guidance and internet resources

**Requests for Feedback on Medical
Device Submissions:
The Pre-Submission Program and
Meetings with Food and Drug
Administration Staff**

**Guidance for Industry and Food
and Drug Administration Staff**

CDRH Programs

- Early Feasibility Study Program
 - **For:** Clinical study of devices at earlier stages of development
 - **Includes:** tools for IDE submitters to develop protocols that adequately mitigate risks at this early stage
- Expedited Access Pathway Program
 - **For:** devices that address unmet medical needs for life threatening or irreversibly debilitating diseases or conditions
 - **Includes:** tools for expediting the development, assessment, and review of these devices

Other FDA Resources

- [CDRH Learn](#)

- IDE Basics
- Early Feasibility Studies
- Clinical Trial Program Updates
- Pre-Submissions
- Many more!



- **Device Advice**

- [Investigational Device Exemptions](#)
- [Expedited Access Pathway](#)



Tips for Successful IDE Submissions

- **IDE Application**

- Follow eCopy guidelines
- Organize clearly (e.g., use a master table of contents with continuous numbering)
- Ensure all required elements are included (see checklist on Device Advice)
- “Tell the Story”
 - Provide basic information to support FDA review
 - Provide rationale for adequacy of data provided
- Be consistent throughout submission
- Address previous FDA submissions, interactions, and feedback

Examples of Basic Questions

- Describe device components and materials
- Describe principle of operation and key characteristics
- Clarify version of device tested compared to version for clinical study
- Clarify what testing was done with rationale
- Provide adequate description of test conditions, success criteria, and results

Tips for Successful IDE Submissions

- **During review**
 - Be available and responsive for interactive review
 - Be aware of review process/timeline
- **After receiving a deficiency letter**
 - Prepare organized response
 - Respond point by point
 - Use numbering in letter

Summary

- IDE regulations encourage discovery and development of medical devices while protecting public health and safety
- IDE applications to FDA are needed for significant risk studies of device safety and effectiveness that are not exempt
- IDE regulations, guidance documents and web resources describe IDE application contents and FDA actions on those applications
- High quality submissions allow reviewers to focus on substantive questions for more efficient review

Resources

- Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors – Medical Devices

www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm

- Frequently Asked Questions About Medical Devices
- Significant Risk and Nonsignificant Risk Medical Device Studies

- Sponsor's Responsibilities For Significant Risk Device Investigations

www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm049859.htm

Resources

- Guidance: FDA Decisions for IDE Clinical Investigations
www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279107.pdf
- Standard Operating Procedures Review of IDE Application-Specific Issues
www.fda.gov/MedicalDevices/deviceregulationandguidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm384135.htm
- Guidance: IDEs for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies
<http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279103.pdf>

Questions

Please complete the session survey:

surveymonkey.com/r/DEV-D1S4

Call to Action

- IDE regulations exist to protect public health and integrity of data while encouraging innovation
 - Keep regulations and requirements in mind
 - Use available resources, including interaction with FDA