

# How Do You Know When an IDE is Required?

**Application Submission Steps for  
Investigators and Research Staff**

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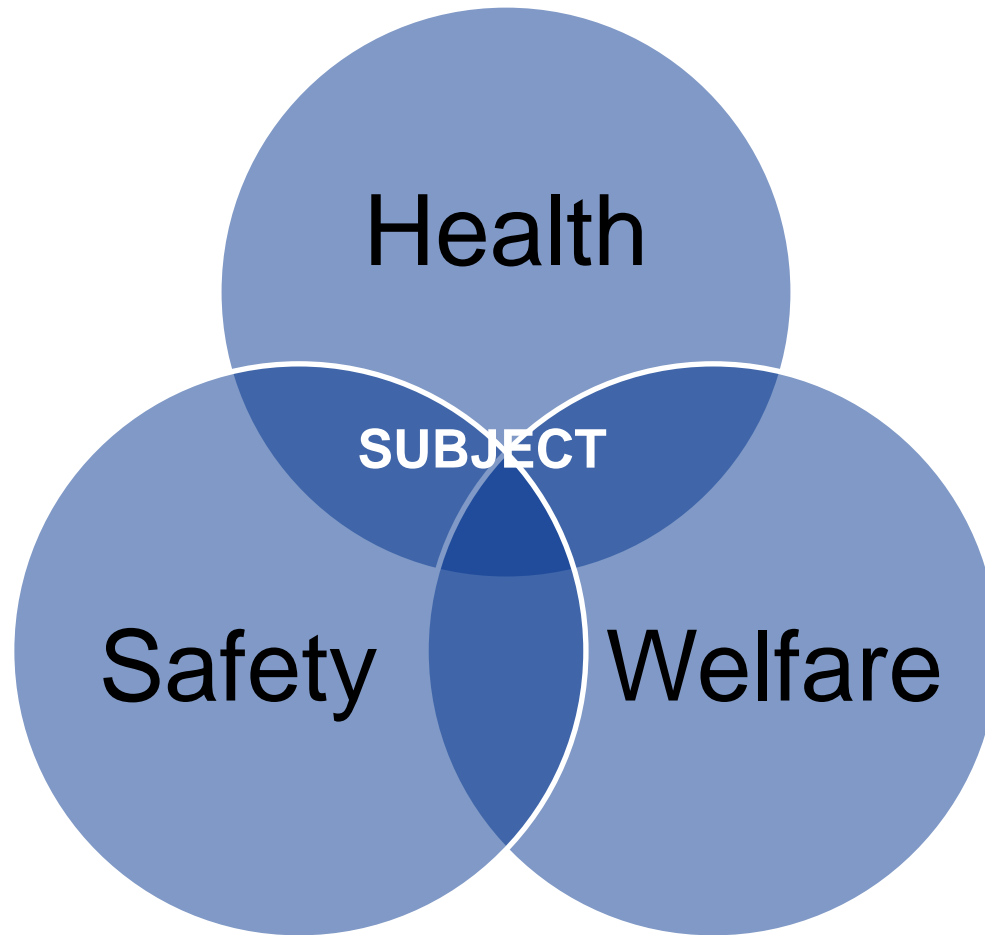
# Agenda

- What are the various classifications for investigational devices?
- How to Determine a Device Classification?
- How to Determine if an IDE is needed?
- What are the essential items for an IDE Application?
- FDA Submission Guidelines and Timelines
- UHCMC IRB Policy Relating to an IDE

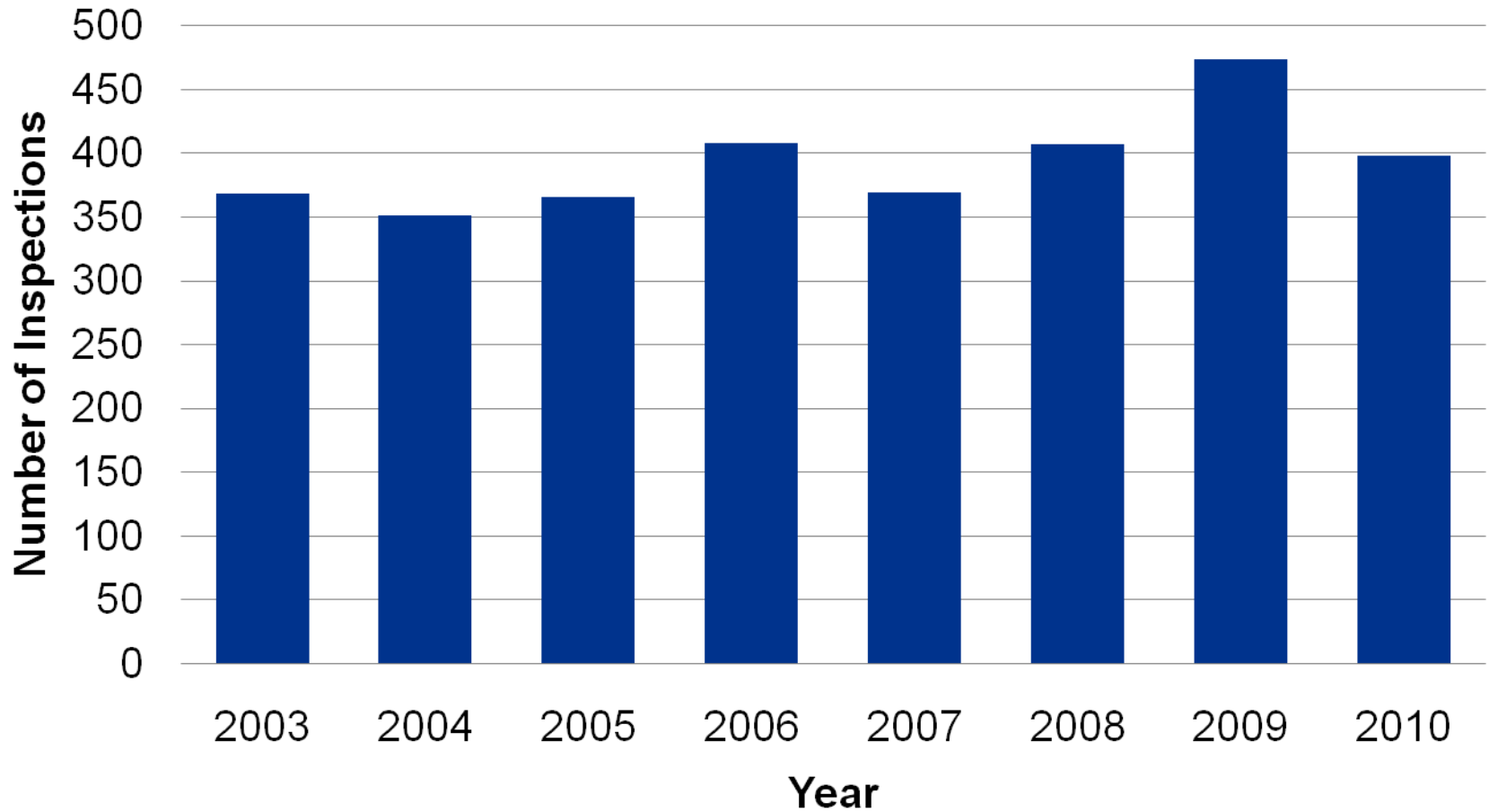
# Learning Objectives

- Learn the differences between a significant and non-significant investigational device
- Acknowledge the appropriate occasion where an IDE is required
- Identify FDA expectations for a complete IDE Application
- Discuss standard FDA submission timelines and application guidelines
- Similarities/differences with UHCMC IRB Policies

# What is most important in human clinical research?

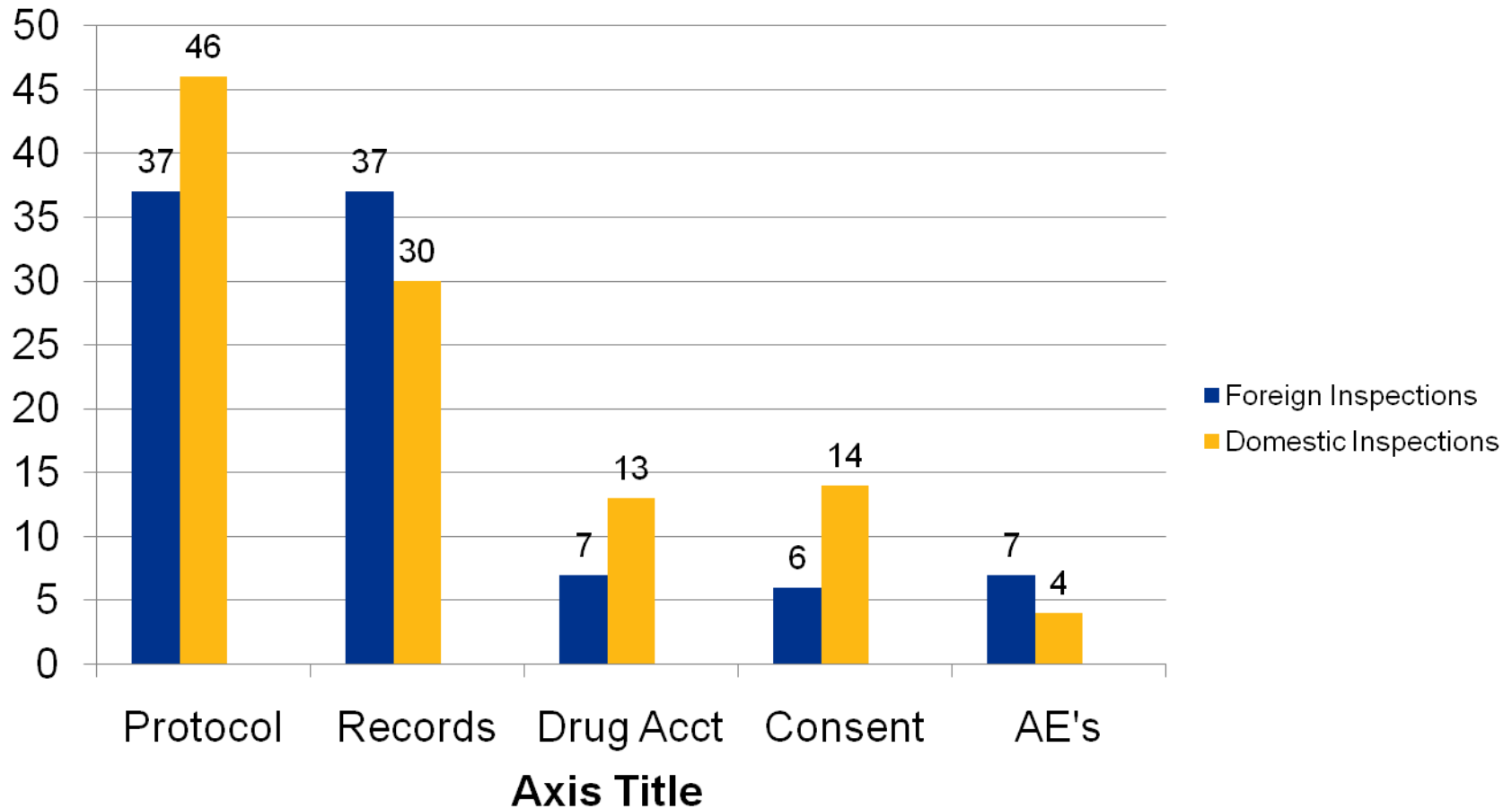


# Clinical Investigator Inspections\* (CDER, FY 2003-2010)



\*Based on inspection start date [4/01/2011]  
Leslie Ball, MD, FDA DSI

# Clinical Investigator Inspections Frequency of Deficiencies\* (CDER, FY 2010)



\*Based on letter issue date; Inspections may have multiple deficiencies, [4/01/2011]

Leslie Ball, MD, FDA DSI

# FDA PI Inspections

- 2006-2010: FDA Warning Letters Investigators
  - **PI Involvement**
  - **PI Engagement**
  - **PI Control of the Study:** Clinical Trial Plan
  - **PI Oversight:** Site, Staff, Satellite Staff
  - **PI Delegation:** To Medically Qualified Staff
  - **PI and Staff Training**

# Helping an Investigator Move From Concept to Reality: Investigational Devices

- To determine the need for an IDE, investigators need to evaluate the following elements:
  - What Class listing does the Device fall under?
    - Class I, II, or III?
  - Intent for Use of the Device
    - What is the Risk vs. Benefit for the participant?
  - Risk Profile of the Device
    - Is the Device a significant risk device?
  - Approved Labeling of the Device
    - Does the device follow the FDA approved labeling?



# What are the Differences in Device Classes....*Assessing the Level of Risk*

- **Class I Devices**
  - Non-Significant Risk
  - Generally does not require the submission of an IDE
  - These devices present minimal potential for harm to the user and are often simpler in design than Class II or Class III devices.
  - Examples include: elastic bandages.
- **Class II Devices**
  - *Generally* Non-Significant Risk
  - Most medical devices are considered Class II devices.
  - Examples of Class II devices include powered wheelchairs and some pregnancy test kits.
- **Class III Devices**
  - These devices usually sustain or support life, are implanted, or present potential unreasonable risk of illness or injury.
  - Examples of Class III devices include implantable pacemakers and breast implants.
  - 10% of medical devices fall under this category.

\*\* Essentially, the classification of device you're dealing with decides the submission path you will take for the FDA

# What is a Significant Risk Device?

## Under 21 CFR 812.3...

### A Significant Risk Device is a Device that:

- Intended as an implant and presents potential for a serious risk to a subject
- Used in supporting or sustaining life
- Presents a potential for serious risk to a subject
- Used in the diagnosing, curing, or treating of a disease
- Used to prevent the impairment of human health

### What is a Non-significant Risk Device?

- *Any device that does not meet the above criteria*

# Who Decides Whether a Device Study is Significant Risk or Non-Significant Risk?

## **\*\*SPONSORS\*\***

- Sponsors are responsible for making the initial risk determination and presenting it to their local IRB.
- FDA is available to assist the sponsor, clinical investigator, and IRB in making the risk determination
  - ***Unless the FDA has already made a risk determination for the study, the IRB must review the sponsors significant risk or non-significant risk determination for every investigational medical device.***
  - ***If the FDA has not already made a decision regarding the risk determination, the local IRB has the right to disagree with a sponsors risk determination, and recommend an IDE application to the FDA.***
  - ***However, if the FDA has already made the Significant Risk or Non-significant risk determination for the study, the agencies determination is FINAL.***

# Differences Between Significant and Non-Significant Risk Devices?

## Significant Risk Devices

- *Must follow all IDE regulations under 21 CFR 812*
- *Must have an IDE application approved by the FDA before proceeding with the study*

## Non-Significant Risk Devices

- *Must follow abbreviated requirements under 21 CFR 812.2 (b)*
- *Do not have to submit an IDE application to FDA*
- *Sponsors and IRB's do not have to report IRB approvals/changes to FDA*
- *IRB serves as FDA's surrogate for review and approval*

# Considerations When Making the Significant Risk and Non-Significant Risk Determination

- What is the basis for the risk determination?
  - *Always remember that the risk determination is based on the proposed USE of the device, and NOT the device alone*
- Will the subject need to undergo an additional procedure as part of the investigational study?
  - *Example: Standard of care procedure associated with a device will need to be changed to investigate the device in a different capacity*
- What is the nature of harm that may result from the device?
  - *Remember that significant risk devices are those that present serious risk to the safety, health, or welfare of the subject*

## Still Unsure.....

- It is not uncommon for sponsor-investigators to still be unsure if their device is significant or if their device requires an IDE submission even after reviewing the applicable information...

*However, never fear because the FDA understands and looks to help sponsor-investigators in such an event*

# The Pre-IDE: An Investigator's Best Friend

If an investigator is unsure if FDA approval is required through an IDE application, the FDA allows the provisional submission of a Pre-IDE Application

- The Pre-IDE application is a condensed version of the larger IDE submission
- The Pre-IDE allows the investigator to present the necessary information regarding their area of concern/confusion in relation to the device
  - Level of Risk Determination
  - Device Classification



# Elements of a Pre-IDE Submission

# The Pre-IDE: An Investigator's Best Friend

- Once the investigator has submitted their Pre-IDE application to the FDA:
  - The agency will respond with a formal acknowledgement letter stating the applications date of receipt
- From the date of receipt, the FDA generally has between 30-60 days to issue their risk analysis decision regarding your device

# The Pre-IDE: A Decision from the Agency

- **IF** the agency responds to the investigator that a full scale IDE application is not needed, the investigator **can proceed** with submission to their local institutional review board

## HOWEVER

- **IF** the agency responds to the investigator and determines that the level of risk associated with the device is considered **significant**, the investigator **must proceed** with the full scale IDE application

# The IDE Application

## A Monumental Task for the Sponsor- Investigator

# IDE Application:

## *A Detailed Process for Investigators*

- The sponsor of a significant risk study must submit a complete IDE application to the FDA.
- There are no pre-printed forms for an IDE application, **however** an IDE application must include certain required information.
  - *The sponsor must demonstrate in the application that there is reason to believe that the risks to human subjects in the proposed protocol are outweighed by the anticipated benefits*
  - *There is potential knowledge to be gained by the investigation*
  - *The investigation is scientifically sound*

# Investigational Device Exemption (IDE)

## 21 CFR Part 812

- In the eyes of the FDA, the individual listed on the IDE is the sponsor of the application
    - And is thus responsible for:
      - Overall conduct of the trial
      - Regulatory Oversight
      - Oversight of all responsible investigators and protocol procedures
      - Overall patient safety
- \*\*It is important to note that financial obligation does not designate as the trial “sponsor”**

# The Cover Letter: Putting Your Best Foot Forward

- The IDE Cover Letter is used in the administrative processing of an IDE application and is generally the FDA's first glance at your device proposal.
  - It is imperative that the cover letter contains all required elements and necessary information regarding your device proposal

**DOUBLE AND TRIPLE CHECK: The FDA can/will reject applications for missing information. They do NOT like to search for information!**

# Required Elements of an IDE Cover Letter

- Statement that the information provided is an original IDE Submission
  - This will alert the agency that there is no existing IDE number and that an original number will need to be issued for your application
- Device Information
  - Device Name
  - Intended use of device
- Sponsor Contact Information
  - Sponsor Name
  - Sponsor Address
  - Secondary Contact Individual (i.e., research coordinator/regulatory coordinator)
  - Telephone and Fax Contact Information



# Required Elements of an IDE Cover Letter (Continued)

## Device Manufacturer Information

- Name
- Address
- Secondary Contact Individual
- Telephone and Fax Contact Information

# Understanding the Language

- 21 CFR Part 812
  - Details and notice of Important language
- Responsible co-investigators will also need to be established
  - Investigators must be qualified by experience, education, and credentialing to be listed on the protocol and to have protocol specific duties delegated to them
  - All co-investigators must submit and disclose all financial information and any financial interest in the product over \$20,000 or \$50,000
  - Investigators must also need to complete investigator agreements

# Application Body: Foundation for Approval

The following items will need to be included in the body of the IDE application for review by the FDA:

- Name and Address of Sponsor
  - The person/individual who's name is listed on the application is considered the "sponsor". Be sure to never confuse financial relationships as the sponsor.
- Report of Prior Investigations
  - Needs to include reports of all prior clinical, animal, and laboratory testing of the device
  - Needs to be comprehensive and adequate to justify the investigation

# Application Body: Foundation for Approval

- Investigational Plan
  - Purpose
    - *Name of Device*
    - *Intended Use of Device*
    - *Objective and Duration of the Investigation*
  - Protocol
    - Describe the methodology AND specific intent for use
    - Must demonstrate the proposals scientific soundness
  - Risk Analysis
    - Analysis of all increased risks to subjects and how the risks will be minimized
    - Description of subject population

# Application Body: Foundation for Approval

- Investigational Plan (contd.)
  - Description of the Device
    - *Be sure to include details on every component, property, and principle of operation*
  - Monitoring Procedures
    - *Sponsor needs to include their written procedures for monitoring the investigation*
    - *Name and address of monitor*
  - Additional Records or Reports

# Application Body: Foundation for Approval

- Description of Methods, Facilities, and Controls used to manufacture, process, package, store and install the device
- Sample Investigator Agreement
  - Please see handout
- Certification that all investigators have signed the agreement
  - ALWAYS remember to keep your documents updated
- Name and Address of Reviewing IRB
  - List IRB Chairman
- Name and Address of any other institution associated with the application
- Copies of all labeling for devices
  - Commercially available or locally manufactured
- Copies of Informed Consent Document

# Report of Priors: Breakdown

Listed as one of the most frequent areas of deficiency in the application, its VERY important to ensure success in this area

- Listing of all relevant publication (adverse or supportive) toward the evaluation of safety of the device
- Copies of all published and unpublished AE Information
- Any items requested by FDA during Pre-IDE process (if applicable)
- If any non-clinical studies are conducted, a statement that the study was conducted according to Good Laboratory Practice (GLP) regulation 21 CFR Part 58.

# Problem Area's for Investigators

## How to Avoid the Pitfalls

- Common Deficiencies with Report of Prior Investigations
  - Laboratory Studies
    - Inadequate submission of methods
    - Inadequate/no submission of summary or conclusions
  - Animal Studies
    - No rationale for animal selection
    - No statistical justification for number of animals
    - Inappropriate follow-up
  - Prior Publications
    - Inadequate search
    - Copies of relevant sources not included
    - No submission of adverse event information



# Problem Area's for Investigators

## How to Avoid the Pitfalls

- Common Deficiencies with Investigational Plan
  - Questionable Scientific Soundness
  - Failure to **clearly** develop and define objectives
  - Inadequate protocol procedures description
  - Failure to identify all risks
    - Directly correlates to incomplete literature search
  - Failure to submit proper monitoring information

# Problem Area's for Investigators

## How to Avoid the Pitfalls

- Common Deficiencies with Design and Manufacturing of Device
  - Inadequate description of device
    - No submission of engineering drawing of device
    - Rationale for device design
    - No submission of device performance expectation
    - No submission of materials
    - No submission of function

# Additional Application Elements

Several other items are required in the formation of an IDE Submission:

- Financial Disclosure Form (3454 and 3455)
  - *Needed for any investigator listed on the application*
- Investigator Agreement
  - *Needed for any investigator listed on the application*
- FDA Form 3674
- Investigator CV's

# Finalizing the Application

## Compiling The Hard Work

IDE Applications must be sent in Triplicate form (2 hard copy and 1 electronic copy) to the following address. The outside labeling should clearly identify the submission as “Original IDE Submission”

Food and Drug Administration  
Center for Devices and Radiological Health  
Document Mail Center- W066-G609  
10903 New Hampshire Avenue  
Silver Spring, Maryland 20993

# The FDA Waiting Game

## When to Expect a Response Regarding an Application

- Once an IDE submission is received and processed with the FDA, an acknowledgement letter will be sent by the agency
  - *Official IDE number will be listed on this letter*
- Reference the “date of receipt” on the Acknowledgement Letter
  - *The FDA will have 30 day time window from the date of receipt to issue the investigator a decision regarding their protocol*
  - *The FDA can issue the following decisions regarding an application:*
    - *Approval*
    - *Approval with Modifications*
    - *Disapproval*

# FDA Determination for an Application

## How to Proceed?

- Issued an Approval
  - *Investigator free to move forward with obtaining approval from their local IRB*
  - *Be sure to make a firm notation of the stamped approval date; as this will dictate your annual report timeframe*
- Issued an Approval with Conditions
  - *Although the FDA has come concerns regarding the application and smaller conditions may be required, an investigator can begin their study; however must respond to the FDA in 45 days*
- Issued a Disapproval
  - *The investigator may not begin the study until an amendment has been submitted to address serious deficiencies in the application*
  - *Once an amendment has been submitted, the FDA 30 time clock begins again*

# Addressing the Changes Items that Require an IDE Modification

## Investigational Plan Changes = FDA Supplement Application

The FDA believes that the following types of protocol changes can have a significant effect on the scientific soundness of a protocol and the validity of the data:

- **Change to the indication**
- **Change in type or nature of study control**
- **Change in primary endpoint**
- **Change in method of statistical analysis**
- **Early termination of the study**

*Any of these changes must be approved by the agency in the form of a supplement; and then approved by your local IRB*

# Addressing the Changes Items that Require an IDE Modification

Also plan to submit an IDE supplement if your investigator plans to initiate the following:

- Increasing the number of investigational sites
- Changing the number of research participants
- Change in primary research investigators
  - Co-investigators
  - Site principal investigator

***All supplements must be submitted in triplicate form, and the labeling must identify the submission as “ Supplemental IDE”.***



## Minor Changes Also Arise.... IDE Annual Report

Because many changes that occur are minor, the following are examples of items that can be submitted at annual report time:

- The purpose of the study
- Risk analysis
- Monitoring procedures
- Labeling
- Informed consent materials
- IRB information

# Somewhere in the Middle...

## 5 Day Notice to the FDA

- Although some changes do not require prior approval from the FDA, some changes need to be documented and submitted to the FDA earlier than the time of annual report.
- If a sponsor makes a change, the sponsor must notify the FDA in writing no later than 5 working days after making the change.
- These notices must be identified as “Notice of IDE change”.

# Somewhere in the Middle...

## 5 Day Notice to the FDA

- The notification must include the following for review by the FDA:
  - Description of change
  - Assessment supporting the conclusion that the change does not significantly impact the study design
  - Supporting information that the change does not affect the rights, safety, and welfare of the subject

*The FDA will notify the sponsor if questions arise or additional information is needed.*

# Policies

## UHCMC Policies Relating to FDA Sponsor-Investigator

- Per UHCMC Policy: Investigational Devices Used in Research, all devices with an Investigational Device Exemption number require full Board approval.
- In accordance with FDA Regulations 21 CFR 812.3, the following requirements are applicable to all UHCMC sponsor-investigators holding an IDE:
  - *Maintaining the IDE*
  - *Obtaining Qualified Investigators and Monitors*
  - *Providing necessary training and education for investigators*
  - *Monitoring the Investigation*
  - *Controlling the investigational product*
  - *Reporting SAE's to FDA and Investigators*
  - *Maintaining accurate records*
  - *Implementing SOP's*

# Policies

## UHCMC Policies Relating to FDA Sponsor-Investigator

When a UHCMC investigator is the sponsor of an IDE, the UHCMC IRB requires the investigator to meet with a representative of the Office of Research Compliance and Education to review their FDA responsibilities as a sponsor investigator.

*Research Staff Education and Training is mandatory per FDA; if you're aware of an investigator beginning an IDE or an IDE that is already in progress, please contact the Office of Research Compliance to ensure proper training.*

**Thank you for Attending Today's Lecture**

Questions??????