Development of an IND/IDE Regulatory Knowledge Support Core

Philip Cola, M.A.
Vice President, Research and Technology

Jenna Stump, MS, CCRP
IND/IDE Regulatory Specialist

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Regulatory Affairs 101: Navigating the FDA Process
Research Landscape: Current Challenges

Challenges that impact Investigators with Investigator-Initiated Research:

– Regulatory and compliance burden

– Recruitment and retention of qualified clinical research personnel

– Economic pressures
Compliance Matters..... For Everyone

In 2012, failure to document clinical research in accordance with GCP resulted in:

- 700 site inspections
- 600 citations
- 5 disqualifications
- Research misconduct (ORI)

(FDA, 2012) (BIMO, 2012)
Why is IND/IDE Research Support so Important?

• Must develop **scientifically sound research** protocols

• Must **navigate FDA** landscape with **efficiency**

• Maintain **compliance** with FDA regulations
  – 21 CFR 11- Electronic Records; Electronic Signatures
  – 21 CFR 312 – Investigational New Drug Application
  – 21 CFR 812 – Investigational Device Exemptions
Finding the Missing Link
Development of an IND/IDE Regulatory Knowledge Support Core
IND/IDE Regulatory Knowledge Support Core

Comprehensive Clinical and Translational Science Collaborative (CTSC) Core

— Established in 2011 at University Hospitals Case Medical Center

Services CTSC investigators and sites across the northeast Ohio region
IND/IDE Regulatory Knowledge Support Core

• Assists investigators from start to finish of the protocol lifecycle

• Level of service flexible to investigators needs

• Promotion of investigator-initiated research growth through fee-for-service mechanism
IND/IDE Regulatory Knowledge Support Core

- Standardize FDA communications for all sites/investigators
- Increase efficiency for study start-up and accuracy of budget creation
- Compliant document submission and storage (21 CRF Part 11)
- Monitoring and education
Reviewing the Model

IND/IDE Regulatory Knowledge Support Core
Investigator-Initiated Research Support—Core Services

Support can begin at any phase: The sooner the better!
Helping an Investigator Move From Concept to Reality: Investigational Drugs and Devices

• To determine the need for an IND or 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 Drug or Device
  • What is the Risk vs. Benefit for the participant?
  • Risk Profile of the Drug or Device
  • Is the Device a significant risk device?
  • Approved Labeling of the Drug or Device
  • Does the device follow the FDA approved labeling?
Considerations For Significant Risk Device 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
IND Exemption Criteria
21 CFR 312.2

• The drug product is lawfully marketed in the United States
• No intent to report the investigation to the FDA as a well-controlled study in support of a new indication
• No intent to use clinical information to support any significant change in the labeling of the drug.
• Investigation is conducted in compliance with IRB review requirements
• Investigation is not intended to promote or commercialize the product
• The investigation does not involve:
  – New Route of Administration
  – New Dose
  – New Patient Population
  – Or other factor that would significantly increase the risk associated with the use of the drug
Considerations for Drug Exemption Determination

- **Dose**: Increases in dose, frequency, or duration of administration, compared to the already approved labeling dose regimens, can be significant increase in the risk.

- **Route of Administration**: The conversion of an oral route of administration to an injectable route could present significant changes.

- **Patient Population**: The known and unknown possibilities can vary considerably across different treatment populations.
Still Unsure
Utilize Pre-IND/IDE Process

The FDA allows the provisional submission of a Pre-IND/IDE Application

- Condensed version of the larger submission
- Allows the investigator to present the necessary information regarding their area of concern/confusion in relation to their drug or device
Still Unsure

Utilize Pre-IND/IDE Process

• From the date of receipt, the FDA generally has between 30-60 days to issue a decision regarding risk OR to book Type-B meeting

• IF a full application is not needed, the investigator can proceed with submission to their local institutional review board

**H owever**

• IF the device is considered significant or use of drug does not fall under exemption, the investigator must proceed with the full application
Investigator-Initiated Research Support

- Protocol Review and Evaluation
  - Pre-IND/IDE Application Assistance
  - Full IND/IDE Application Assistance

- IND/IDE Electronic Application/Binder System
  - FDA Review of Pre-IND/IDE Application
  - FDA Approval of Full IND/IDE Application

- Study Start Up
  - PI Training
  - Team Training
  - CRF Creation
  - Assistance with Electronic Regulatory Binder
  - Monitoring Plan & Evaluation

- Protocol Maintenance, Reporting & Assistance
  - Monitoring
  - Reports to FDA
  - Final Report to FDA and Study Closeout
RegulatoryBinder
Piloted FDA Software System

Electronic IND/IDE Documentation Software System

Developed at Case Western Reserve University and piloted at UHCMC as a hosted cloud application

Piloted in 2011 for all investigators utilizing Investigator Initiated Research Core

FDA Submission and application cataloging tool

Comprehensive eRegulatory Binder storage system
RegulatoryBinder

Piloted FDA Software System

• Secure, Part 11 complaint storage (FDA Requirement)
• Expedites regulatory documents and assigns tasks
• Generates standard FDA documents
• Exports to interactive PDF to be eSigned and submitted to FDA
The IND/IDE Application
A Monumental Task for the Sponsor-Investigator
Drug and Device Applications: A Detailed Process for Investigators

• The sponsor of a significant risk study must submit a complete IND or IDE application to the FDA.

➢ 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
In the eyes of the FDA, the individual listed on the IND or 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”**
Additional Application Elements

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

• Statement of Investigator (1572)
• 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 (if applicable)
• Investigator CV’s
The FDA Waiting Game
When to Expect a Response Regarding an Application

• Once an IND/IDE submission is received and processed with the FDA, an acknowledgement letter will be sent by the agency
  – *Official application 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
Upon Approval of an IND/IDE......

Never Forget

The approval of an application is just the BEGINNING

An investigator must never forget that an IND/IDE application is a “living” project that must be constantly monitored, updated, and nurtured from approval to closure to maintain compliance
IND and IDE Study Start-up and Maintenance

Continued Support Through the Research Core
Study Start-up

- **Sponsor Training**
  - One on One
  - Regulations
  - Sponsor Responsibilities
    - Team
    - Reporting
    - Oversight
    - Sponsor hat vs. investigator hat
  - Protocol
  - Informed Consent

- **SIV/Research Team Training**
  - Protocol
  - Informed consent
  - Delegation of duties
  - Recruitment
  - Subject safety
  - Compliance and regulatory documentation
Protocol Maintenance and Reporting

• Reporting assistance for duration of trial
  – Annual Report
  – Deviation
  – Med Watch
  – Amendment

• Comprehensive Maintenance
  – Investigator/specialist one-on-one meetings
  – Review of any changes
  – Establishment of team meetings
The Submission of a Progress Report (Annual Report) to the FDA

• An investigator must always remember that the progress report date is based on the approval date, which will be stamped on the top of the approval letter (as follows):

**IND/IDE Number:** X160041

**Indications for Use:**

Dated: January 1, 2012

Received: January 10, 2012

CMS Reimbursement Category: B4

Annual Report Due: One Year From the **Stamped Date** of this Letter
Minor Changes Also Arise....
IND/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
Med Watch Reporting Form 3500

How to Complete the Process of Serious Adverse Event Submission to the FDA
The Med Watch process is intended to report serious adverse events for human medical events associated with the use of:

- FDA-regulated drugs,
- Biologics (including human cells, tissues, and cellular and tissue-based products)
- Medical devices (including in vitro diagnostics)

Med Watch forms can be submitted via fax, facsimile, or online. Be sure to keep a copy of the form for regulatory binder.
What NOT to Report to the Med Watch System:

- **Vaccines:** Report vaccine events to the Vaccine Adverse Event Reporting System (VAERS) online at https://secure.vaers.org/VaersDataEntryintro.htm

- **Investigational (study) drugs:** Report investigational (study) drug adverse events as required in the study protocol to the FDA
Med Watch Reporting Form 3500
Reporting Differences

- **Form FDA 3500: Voluntary Reporting**

  For use by healthcare professionals, consumers, and patients.

- **Form FDA 3500A: Mandatory Reporting**

  For use by IND reporters, manufacturers, distributors, importers
FDA Guidance Documents

How to Navigate the Documents to Retrieve Useful Information
FDA Guidance Documents
Using Their Content to the Advantage of the Sponsor

Good Guidance Practice (GCP) documents are prepared for industry and the public that relate to:

1) Processing, content, and evaluation of regulatory submissions
2) Design, production, manufacturing, and testing of products
3) Inspection and enforcement of polices and procedures
FDA Guidance Documents
Using Their Content to the Advantage of the Sponsor

Always Remember: Guidance Documents to NOT exist to bind the FDA to a particular thought or suggestion.

They are merely tools to help the investigator/sponsor/research staff to better interpret particular sections of the Code of Federal Regulations.
Conception to Implementation
Results of Research Support Core Assistance

To date, the Investigator-Initiated Research Core have:

- Participated in the start-up, management, or maintenance of 30 IND/IDE protocols based across 13 clinical departments at 3 CTSC Institutions

- Provided overall support to more than 26 sponsor investigators.

- Conducted FDA educational sessions for UHCMC Research Community
Investigator-Initiated Research Support Core Activities as of September 2013

New IND/IDE Projects

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Thank you for Attending Today’s Lecture

Questions?