Investigator-Initiated INDs

Conduits

INSTITUTES FOR TRANSLATIONAL SCIENCES

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PPHS/IRB
Research Grand Rounds
Outline of Presentation

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What is an IND?

• Investigational New Drug

• Alerts the FDA
“The FDA disapproves of its first drug”
IND Regulations - 21 CFR 312

Title 21 CFR Part 312

• Contains procedures and requirements governing the use of investigational new drugs and biologics
IND required for

1. Studies involving investigational drugs or biological products not approved by the FDA, or

2. Studies using approved drugs/biologics *but*
   • for new indications or populations not in the approved labeling, or
   • as new formulations or with new routes of administration, or
   • in new dosages that significantly increase risks (or decrease the acceptability of the risks)
IND Exemptions
IND Exemptions

A clinical investigation may be exempt from IND requirements if ALL of the following criteria are met......
IND Exemptions (cont.)

1. *if* the drug product is lawfully marketed in the United States;
2. *if* there is no intent to report the investigation to FDA as a well-controlled study in support of a new indication and no intent to use it to support any other significant change in the labeling of the drug;
3. *if* in the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug;
IND Exemptions (cont.)

4. *if* the investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product;

5. *if* the investigation is conducted in compliance with the requirements for review by an IRB and with the requirements for informed consent; **AND**

6. *if* the investigation is not intended to promote or commercialize the drug product).
What is a Sponsor/Investigator of an IND?

1. The person who applies for and receives an IND is the ‘holder of the IND’

2. Differs from a pharmaceutical company or governmental agency sponsor

3. Often has a dual role as the PI and the sponsor
Confusion Over Who ‘Holds’ the IND

1. The pharmaceutical company who supplies the study drug/placeto?
2. What if there are 2 co-PI’s?
Roles and Responsibilities Sponsor/Investigator

1. Initiates the clinical investigation
2. Selects qualified investigators
3. Provides study team with the information they need to conduct an investigation properly
4. Ensures proper monitoring of the investigation
Roles and Responsibilities (cont.)

5. Ensures that the trial is conducted in accordance with the protocol

6. Ensures that FDA and all participating investigators are promptly informed of significant new AEs or risks

7. Assumes responsibility for the proper dispensation, administration & disposal of the investigational drug
IND Application Resources

Forms

• http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm

FDA Web Site

• http://www.fda.gov/Drugs/default.htm
IND Application

FDA Jurisdiction of Products

**CDER Regulates:**

- Drugs
- Monoclonal antibodies for in-vivo use
- Proteins intended for therapeutic use
- Growth Factors
- Immunomodulators

**CBER Regulates:**

- Cellular Products
- Vaccines
- Allergenic extracts
- Blood and blood components
- Gene Therapy products
Pre IND Consultation

FDA Consultation Prior to Application

• Pre IND Consult with FDA
  – Occurs within 60 days of receipt of request
  – Typically, only one meeting per issue
  – One hour formal meeting by telephone
  – FDA issues official minutes

21 CFR 312.82
IND Application

1. No FDA application ‘form’
2. Cover letter (Not required by CFR)
3. Form FDA 1571
4. Form FDA 1572
5. Table of Contents
6. Form FDA 3454
IND Application (cont.)

7. Form FDA 3674
8. Introduction statement and general investigational plan (Where you are headed)
9. Investigator’s Brochure (preliminary package insert--if available)
10. Protocol (plan for collecting safety/efficacy data)
11. Chemistry and manufacturing information
12. Environmental assessment or claim of categorical exclusion,

13. Pharmacology/toxicology data/risks (to conclude that it is reasonably safe to conduct the proposed study)

14. Previous human experience (same or similar products)

15. Letter of Cross Reference, if applicable

21 CFR 312.23 (a)
“Oh great. Now the FDA is regulating safety coated caplets of eyes of newt!”
FDA Forms
Form 1571

1. The Sponsor/Investigator agrees to wait 30 days before beginning the study

2. Will not begin or continue the study if placed on clinical hold

3. IRB will be responsible for review and approval of the study

4. Conduct the study in accordance with all applicable regulatory requirements

5. Accompanies all correspondence to the FDA
Form 3454

Attest to the lack of financial interest on the part of the sponsor-investigator and of all clinical investigators connected to the study.
Form 1572

- The investigator promises to conduct the study in accordance with the protocol

- To personally supervise or conduct the investigation

- To inform the subjects of the investigational status of the test article

- To report adverse events to the sponsor

- To read and understand the Investigational Brochure

- To inform all support personnel of the investigation requirements
Form 1572 (cont.)

• To maintain adequate records and make them available for inspection

• To assure that the IRB is in compliance

• To assume responsibility for initial and continuing review by the IRB

• To promptly report study changes and unanticipated risks to the IRB

• Not make changes in the research without IRB approval

• To comply with the requirements regarding the obligations of clinical investigators
IND Application Format

• 3 copies (An original and 2 copies)
• 1571 Numbering: for the initial IND, serial numbering begins with ‘0000’ and increases by 1 with each submission to the FDA
• Keep a copy for your IND regulatory file
• Send by overnight UPS or FedEx
FDA Receipt of IND

1. Issuance of the IND #
2. Reviewing division
3. 30 days
4. ‘May proceed’ notification (by letter or e-mail)
Clinical Hold

Order issued by FDA to sponsor to delay a proposed clinical investigation or suspend an ongoing investigation

21 CFR 312.42
Reasons for Clinical Hold

Phase I:
• Unreasonable and significant risk
• Clinical investigators not qualified
• Inadequate IB
• Insufficient information to assess risk

Phase 2/3:
• Protocol design inadequate to meet objectives
IND Submissions Common Pitfalls

• Data lacking to support dose proposed
• Inadequate report of prior investigations
• Questionable scientific soundness
• Poorly defined stopping rules
• Undefined statistical analysis
• Undefined endpoint
Keeping IND Current

The sponsor-investigator agrees to keep the IND current by conforming to all responsibilities as per 21 CFR 312.50 which include:

- monitoring safety/efficacy;
- conducting site visits/monitoring other sites (if multi-site);
- maintaining adequate records for study drug;
Keeping IND Current (cont.)

- maintaining regulatory documents and case report forms with accompanying source records;
- maintaining safety reports (FDA Form 3500a Medwatch);
- submitting any protocol amendments regarding safety to the FDA; and
- providing annual progress reports.
IND Amendments

1. Protocol Amendment (21 CFR 312.30)
2. Informational Amendment (21 CFR 312.31)
3. Safety reports (21 CFR 312.32)
4. Annual Reports (21 CFR 312.33)
IND Amendments Safety Reports

New AE reporting rules as of 3/28/11 (21 CFR 312.32)

1. Report an AE to the FDA only if there is evidence to suggest a causal relationship between the study product and the AE

Other instances of reporting:

• A single occurrence, uncommon, strongly associated with drug exposure

• 1 or more occurrences, not commonly associated with drug exposure but uncommon in the population being studied
Safety Reports (cont.)

• Aggregate analysis of specific AEs that indicates a higher frequency in the drug treatment group than in concurrent or historical control group

• Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or cardiogenicity

• SAEs
Safety Reports (cont.)

• Sponsor/Investigators must promptly review all data relevant to the safety of the drug from any source, foreign or domestic
Safety Reports (cont.)

IND Safety Reports

- Each AE notification shall be made as soon as possible and no later than 15 days after the sponsor’s initial receipt of the information; SAEs ASAP but within 7 calendar days (by fax or phone)

- Each written notification may be submitted on FDA Form 3500a or in a narrative format

\[21 \text{ CFR } 312.32\]
Annual Reports

1. Sponsor/Investigator required responsibility
2. Within 60 days of the anniversary date of the IND’s ‘may proceed’ notification
3. Study title, protocol, objectives, status, number of subjects planned versus enrolled, completed and discontinued, and description of results
4. Summary: narrative or tabular reporting of SAEs, frequent and most serious by body system, summary of IND safety reports for the year, number of subjects expired and cause of death, revised IB or protocol.

21 CFR 312.33
Essential Documents for the Regulatory Binder

- Signed Protocol and Amendments
- Investigator Brochure
- FDA Form 1572
- Curriculum Vitae
- IRB Membership List
- Laboratory Certifications, lab ranges
- Financial Conflict of Interest
- Investigational Product Accountability
- Delegation of Authority Log
- Serious Adverse Events
- Communication/Correspondence from IRB
- Screening/Enrollment Log
Supply/Handling of Investigational Product

1. Supply investigator with investigational product after all required documents are obtained, if a multi-site study

2. Provide written procedures for handling and storage of investigational product

3. Ensure timely delivery of product and maintain all records related to shipment, receipt, disposition, return, and destruction of the product

4. Maintain a system for disposition of unused product
Closing an IND

• An IND may be inactivated at the request of the Sponsor/Investigator and may be reactivated with proper documentation.
• The FDA may terminate an IND that has been inactive for over 5 years.
• An IND can be withdrawn at the Sponsor/Investigator’s request. The IND cannot be reactivated, but can only be resumed with a new IND.
The sponsor shall notify the FDA within thirty working days of completion or termination of investigation. Sponsor shall notify IRB and participating investigators within 6 months after completion or termination.
Clinicaltrials.gov Form FDA 3674

It is the responsibility of the Sponsor/Investigator to obtain a personal clinicaltrials.gov account, to post the trial and to make timely updates.

Apply for an ‘individual account’ through the Protocol Registration System (PRS)

http://prsinfo.clinicaltrials.gov/
Any Questions?
Thank you!

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