FDA Investigational New Drug Studies (IND) Studies

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Learning Objectives

♦ Define Drug

♦ Understand IND regulations and associated guidances and identify where both are located

♦ Define IND and identify when an IND is required
Learning Objectives

♦ Recognize who is a Sponsor, who is an Investigator, and the responsibilities associated with each role

♦ Know what information is required to be submitted in an IND Application

♦ Understand IND management activities
What is a Drug?

A drug is defined as a substance that is:

- recognized in the official US Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary
- intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animal
- intended to affect the structure or any function of the body of man or other animals (other than food)

Reference: Federal Food, Drug and Cosmetic Act (FC&C Act)
What is an IND?

An IND is a request for Food and Drug Administration (FDA) authorization to administer an investigational drug to human subjects.

- The FDA regulations pertaining to an Investigational New Drug Application can be located in 21 CFR 312
- The FDA regulations pertaining to human subject research can be located in 21 CFR 54 (Financial Disclosures by Investigators) and 21 CFR 56 (Institutional Review Boards)
Types of INDs

- **Investigator IND**
  - submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed.

- **Emergency Use IND**
  - FDA authorizes the use of an experimental drug in an emergency situation that does not allow time for submission of an IND. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.

- **Treatment IND**
  - submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

Reference:
http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm
IND Exemptions

A clinical trial investigating FDA approved marketed drug products can be exempt, provided the trial meets all of the following:

- The study is not intended to support a new indication or other labeling change.
- The study will not support "significant" advertising changes.
- The drug maintains lawful marketing status.
IND Exemptions

- The study does not involve a route of administration, dosage level, patient population, or other factors that significantly increases the risks.

- The study is otherwise compliant with all requirements under 21 CFR 56 (institutional review board) and 21 CFR 50 (informed consent).

Reference: 21 CFR 312.2
Phases of Clinical Investigations

♦ Phase I Studies
  • Evaluate the investigational product for safety in a small number of healthy volunteers

♦ Phase II Studies
  • Evaluate therapeutic efficacy, safety, and short-term side effects are studied in subjects who have a specific disease or condition

♦ Phase III Studies
  • Large scale studies to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population
IND Exemption Process

An IND exemption may be obtained from:

- The Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) for all IND cancer trials
- The Radioactive Drug Research Committee (RDRC) for any radio isotopes
- The Office of Clinical Research (OCR) for all potential INDs
- The Food and Drug Administration (FDA) for all potential INDs
Definitions

IND Sponsor
A sponsor is an individual, company, institution, or organization that takes responsibility for and initiates a clinical study

Reference: 21 CFR 312.3(b), 312.50
Definitions

**Investigator**
An investigator is an individual under whose immediate direction the study drug is administered or dispensed. If a team is involved, the leader is the investigator; other team members are sub-investigators.

**Co-investigator**
Has same responsibility as Investigator

Reference: 21 CFR 312(b), 312.60
Sponsor Responsibilities

♦ Obtain FDA authorization of IND application prior to study start

♦ Ensure IRB approval is obtained

♦ Select qualified investigators and vendors
  • Obtain signed Form FDA 1572, CVs, current U.S. medical licenses, and financial disclosure information from all investigators
  • Confirm each Investigator has obtained IRB approval and ensure each IRB is registered (IRB compliance with part 56) with HHS
  • Obtain signed contractual agreement with vendors
Sponsor Responsibilities

♦ Provide each clinical investigator with adequate information about the drug

♦ Clearly document each Sponsor staff member’s responsibility along with his/her qualifications

♦ Ensure investigation is conducted in accordance with the current protocol
  • Train all staff on relevant information needed to conduct the study and ensure new information is provided

♦ Manage investigator noncompliance
Sponsor Responsibilities

♦ Monitor the investigation

♦ Ensure all significant new information is promptly communicated to the FDA and each IRB

♦ Select qualified monitors and ensure proper monitoring of the investigation

♦ Evaluate any adverse events

♦ Control the investigational product and ensure it is properly labeled

♦ Maintain accurate, complete, and current records
Sponsor Responsibilities

♦ Register applicable trials on ClinicalTrials.gov
♦ Ensure timely submissions to the FDA
♦ Ensure a final Clinical Study Report is issued no later than one year from the study close date
♦ Withdraw or inactivate the IND after the completion of all trials

Reference: 21 CFR 312.50-59
PSOM Sponsor Qualifications

- Member of PSOM standing faculty
- Physician/Dentist with current US license or has a licensed individual to review safety
- Experience with FDA-regulated clinical research
- Successful completion of OCR Sponsor training
- Availability of adequate resources
- No continuing non-compliance with clinical trial oversight or conduct
- No significant financial conflict of interest (fCOI) related to the IND or the clinical trial
- Not a direct report of a Penn faculty member who has a significant fCOI relative to the clinical trial or the IND
Selecting Qualified Investigators

- Ensure they are not disqualified and/or restricted by the FDA
  - Check the database:
    [www.fda.gov/ICECI/EnforcementActions/UCM321308](http://www.fda.gov/ICECI/EnforcementActions/UCM321308)

- Obtain from each prior to allowing participation:
  - Signed 1572’s
  - CV, additional statement of qualifications
  - Current US professional license (medical, nursing, etc.)
  - Financial disclosure information
  - Ensure each IRB is registered with DHHS
Selecting Qualified Investigators

- Document qualifications of each investigator
  - Based on training and experience
  - Ensure each investigator remains qualified throughout the study
Investigator Responsibilities

♦ Protect rights, safety, welfare of subjects
♦ Ensure investigation is conducted according to signed Form FDA 1572, investigational plan, applicable regulations
♦ Ensure informed consent is obtained
♦ Communicate appropriately with the Sponsor, IRB, and research team
Investigator Responsibilities

♦ Control of the investigational product
♦ Disclose accurate financial information to the Sponsor
♦ Maintain accurate, complete, and current records

Reference: 21 CFR 312.60-69
Financial Information

❖ Sponsor

• Must collect financial information from Investigators
  – Before permitting to participate in the study AND remind Investigator to report any fCOI change

❖ Investigator

• Must disclose financial information to the Sponsor
  – Before beginning participation in the study AND report fCOI changes to the Sponsor at any time during the study and up to 12 months following the study

References:
21 CFR 54 and Penn policy: http://www.upenn.edu/almanac/volumes/v59/n02/pdf_n02/090412-Supplement-ConflictsInterest.pdf
IND Application Template

- IND Application template, cover letter template, and application instructions are available from the OCR.

Office of Clinical Research
IND/IDE Support Unit
8041 Maloney Building
(215) 746-8334
ocr@exchange.upenn.edu
IND Application Content

♦ Cover letter
♦ Form FDA 1571
♦ Form(s) FDA 1572
♦ Form FDA 3674
♦ Table of Contents
♦ Introductory statement and General Investigational Plan
♦ Investigator’s brochure (IB)
IND Application Content

♦ Protocol(s)
♦ Quality information
♦ Pharmacology and toxicology information
♦ Previous human experience with the investigational product(s)
♦ Additional information
♦ Other relevant information

Reference: 21 CFR 312.23
FDA Forms

Form 1571
- Submitted with initial IND application and all subsequent submissions to the FDA
- The initial IND is required to be numbered 0000
- Each subsequent submission is required to be numbered chronologically in sequence

Form 1572
- Statement of Investigator
- Required for all principal investigators from participating sites

Form 3674
- Certification that Sponsor will register applicable trial on ClinicalTrials.gov
ClinicalTrials.gov

- Responsible party
  - Sponsor, unless designates another individual
- “Applicable clinical trials” must be registered

Clinical Investigation (interventional) + Controlled + FDA-regulated product + Not Phase I = Applicable Clinical Trial

- Update as per regulation
ClinicalTrials.gov

A service of the U.S. National Institutes of Health

ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. Learn more about clinical studies and about this site, including relevant history, policies, and laws.

ClinicalTrials.gov currently lists 175,894 studies with locations in all 50 states and in 187 countries.

Search for Studies
Example: "Heart attack" AND "Los Angeles".
Advanced Search See Studies by Topic See Studies on a Map

Search Help
- How to search
- How to find results of studies
- How to read a study record

Locations of Recruiting Studies
- Non-U.S. Only (51%)
- U.S. Only (43%)
- Both U.S. and Non-U.S. (6%)

Total N = 33,717 studies
Data as of October 02, 2014

Learn More
- ClinicalTrials.gov Online Training
- Glossary of common site terms
- For the Press
- Using our RSS Feeds
IND Content

Introductory Statement and General Investigational Plan

• A brief introductory statement including name of the drug, active ingredients, pharmacological class, route of administration, planned study duration

• Brief summary of previous human experience, referring to other INDs or marketing experience in other countries

• A brief description of the overall investigational plan for the following year:
IND Content

Investigator’s Brochure

• A compilation of the clinical and nonclinical data on the investigational product that is relevant to the study
• Provide to each participating clinical investigator
• Studies of marketed products may refer to the product label provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator
Protocol(s)

- A protocol for each planned study
- Includes the objective(s), design, methodology, statistical considerations, and organization of a study
- May include the background and rationale for the study
IND Content

Quality Information

• Includes the information relevant to manufacturing, testing, and packaging of the investigational product.

• Must assure proper identification, quality, purity, and strength of the drug substance (active ingredient) and the investigational product.

• IND studies using a marketed product may refer to the product label if the investigational product will be used as per the current label
  
  – Current labels for FDA approved products can be located at:

IND Content

Pharmacology/Toxicology

• IND studies of marketed products may refer to the current product label if the data from the nonclinical studies are sufficient to establish the investigational product is safe for use.

• Adequate non-clinical animal studies on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed investigation.

• Summary of pharmacological and toxicological effects of the drug from completed non-clinical studies.
Previous human experience

• If the investigational product has been previously investigated or marketed, either in the United States or other countries, include detailed information relevant to the safety and efficacy of the proposed investigation.

• Include any published material (provided in full) relevant to the safety of the proposed investigation or to an assessment of the drug's effectiveness for its proposed investigational use.
Previous Human Experience

- If the drug has been marketed outside the United States, a list of the countries in which the drug has been marketed and a list of the countries in which the drug has been withdrawn from marketing for reasons potentially related to safety or effectiveness
Pre-IND Meeting

Prior to the submission of the initial IND, the Sponsor may request a meeting with FDA-reviewing officials.

- The meeting provides an opportunity to determine if the non-clinical information is adequate to support a study in humans and to discuss the scope and design of the study (Phase 1 and 2 studies)

Pre-IND meetings occur within 60 days of FDA receipt of the meeting request

Complete background package is submitted to FDA at least 4 weeks prior to meeting date

Reference: 21 CFR 312.47
Reference: Guidance for Industry: Formal Meetings between FDA and Sponsors or Applicants
Submitting an IND

- IND Sponsor and/or Sponsor Rep must be located in the U.S.
- IND Sponsor must submit the IND application
  - Unless authorization in writing for another to submit on their behalf

Paper
- Submit an original and two copies, together with any accompanying materials, by mail

Electronically
- Copy submitted through Electronic Submissions Gateway (ESG)
  
  ESG = central transmission point for accepting secure electronic regulatory submissions over the Internet
FDA Review of IND Applications

The FDA reviews the data submitted in the IND application to determine the following:

• Does the non-clinical data show the investigational product is safe?
• Does the protocol for the proposed clinical trial expose subjects to unnecessary risks?
FDA Actions on IND Applications

An IND is effective 30 days after the submission has been received by FDA unless FDA has requested modifications.

- If modifications have not been adequately addressed within 30 day time frame, FDA will place the IND on clinical hold
- No studies may proceed until a clinical hold is lifted.

Reference: 21 CFR 312.40
Trial Master File (TMF)

- Sponsor’s records for the IND and the clinical trial
- Keep all essential documents
  - OCR template
- Best practices
  - Update on a regular basis
  - “If it’s not documented, it hasn’t happened.”
- OCR can assist in developing and/or review your current TMF
Trial Master File

- Protocol
- ICF/HIPAA
- Investigational product
- Case Report Forms
- Monitoring
- Adverse Events and Adverse Device Effects
- FDA submissions
- Other agency submissions
- Contractual agreements
- Vendor qualifications
- Sponsor personnel
- Other documents
IND Management Activities

- Protocol Amendments
- Information Amendments
- Investigational Product Management
- Study Monitoring
- Safety Reports
- IND Annual Report
Protocol Amendments

Change in protocol that significantly affects the safety of subjects, scope of the investigation, or scientific quality of the study

- Must be submitted to the FDA before changes are implemented
- Must have IRB approval before changes are implemented

Reference: 21 CFR 312.30
Protocol Amendments

♦ New Protocol
  • Must be submitted to the FDA for review
  • Must have IRB approval before changes are implemented

♦ New Investigator
  • FDA must be notified of the new investigator within 30 days of them enrolling their first subject
Information Amendments

Information amendments advise the FDA of:

- New toxicology, quality, or other technical information
- Notice of the discontinuance of a clinical investigation

Reference: 21 CFR 312.31
Submitting IND Amendments

- FDA Form 1571
- Amendment type and purpose (ex., Protocol Amendment: New Protocol)
- Any supporting information (ex., references to support protocol changes, new investigator qualifications, etc.)
  - A sponsor shall submit a protocol amendment for a new protocol or a change in protocol before its implementation
  - Information amendments and protocol amendments for new investigators are submitted at 30 day intervals (whenever possible)
IND Submissions

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<tr>
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<td>Clinical</td>
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<tr>
<td>PMR/PMC Protocol</td>
<td>Clinical Pharmacology</td>
<td>Formal Dispute Resolution</td>
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11. This submission contains the following (Select all that apply)

- Initial Investigational New Drug Application (IND)
- Request For Reactivation Or Reinstatement
- Development Safety Update Report (DSUR)
- Other (Specify):
**Investigational Product Management**

- Allow access only to qualified investigators
- Supervise all use
- Retain all relevant information
- Record accountability
- Document all changes
Monitoring

- Determine approach and method
- Develop a monitoring plan
- Select a qualified monitor
- Manage non-compliance
An IND Safety Report is an expedited, written notification to the FDA of an adverse experience associated with or potentially associated with the use of an investigational product that is both serious and unexpected

- Serious, related and unexpected adverse events are to be reported to FDA in writing within 15 days of knowledge of the event
- Life-threatening or death that is unexpected and related is to be reported within 7 days by phone or fax

Reference: 21CFR 312.32; Guidance for Industry: Safety Reports Requirements for IND’s and BA/BE Studies
Expedited Safety Reporting

- Serious Adverse Events (SAEs) or new risks associated with the use of the investigational product

- Reporting requirements:
  - Form FDA 1571
  - Form FDA 3500A or CIOMS I
  - Include all available information, including a brief narrative describing the suspected adverse event and any other relevant information
  - If applicable, include identification of similar reports and an analysis of the significance of the suspected adverse event

Reference: 21 CFR 312.32
Expedited Safety Reporting

- Information necessary to evaluate the suspected adverse event may be missing or unknown at the time the initial report is submitted
  - The Sponsor actively seeks information
  - Any relevant additional information that the sponsor obtains must be submitted as a Follow-up IND Safety Report as soon as the information is available
  - Submit no later than 15 calendar days after the Sponsor receives the information.

- Refer to the Penn Manual for time frames

Reference: 21 CFR 312.32(d)(2)
# Expedited Safety Reporting

## IND/IDE Sponsor FDA Safety and Expedited Reporting Requirements

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<th>FDA Reporting Requirements</th>
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<td>Serial</td>
<td>Drug/Device Related</td>
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**Other Events**

- Findings from clinical, epidemiological, or pooled analyses of multiple studies or any findings from animal or in vitro testing that suggests a significant risk in humans exposed to the drug

Reference:

[https://somapps.med.upenn.edu/pennmanual/secure/pm/reporting#SafetyandExpeditedReportingCharts](https://somapps.med.upenn.edu/pennmanual/secure/pm/reporting#SafetyandExpeditedReportingCharts)
Sponsor Reports

- Unanticipated adverse events
- Withdrawal of IRB approval
- Withdrawal of FDA approval
- Current List of Investigators
- Recalls and Drug Disposition
- IND Annual Report
- Informed Consent
- Final Report
- Other Reports
Investigator reports

- Progress report
- Unanticipated adverse events
- Deviations
- Use of investigational product without informed consent
- Withdrawal of IRB approval
- Final report
- Other reports
IND Annual Report

An IND Annual Report is a report of the progress of studies conducted under an IND which is due annually to the FDA

- Submit the report and form FDA 1571 within 60 days of the anniversary of the date that the IND went into effect

Reference: 21 CFR 312.33
The IND Annual Report Contains:

- Previous year's clinical and nonclinical investigations summary
- Summary of the status of each study in progress and each study completed
- Update on the general investigational plan for the next year
- Description of any updates made to the investigational brochure
- Significant protocol modifications not previously reported in an IND protocol amendment
- Summary of any foreign marketing developments during the past year
21 CFR 312

ELECTRONIC CODE OF FEDERAL REGULATIONS

Title 21
Food and Drugs

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OCR Resources and Services

- OCR Website
  - http://www.med.upenn.edu/ocr/
- Penn Manual
  - https://somapps.med.upenn.edu/pennmanual/secure/
- Tools and Templates
- Sponsor Training
- Consulting Services
Thank You

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