Institutional Review Board

Human Research Seminar Series

IND/IDE Requirements

Tuesday, April 16, 2013

Presented by:
David Wallach, CIP
Director
# TABLE OF CONTENTS

IND IDE Requirements ........................................................................................................ 1

Investigational Drug, Biologic and Device Policy ............................................................ 23
Science at the heart of medicine

Einstein Institutional Review Board (IRB)

Human Research Seminar Series
IND/IDE Requirements

Presented by:
David Wallach, CIP, Director

Acknowledgements

Significant contributions to this presentation were made by:

> Kathleen O’Connor, RN, BSN, CIP
  OM Analyst
  Einstein IRB

> Amanda Hammond, JD
  Deputy Director
  Office for the Protection of Research Subjects
  Dana-Farber Cancer Institute
  Dana-Farber/Harvard Cancer Center

> Christine Drabick, MS
  Consumer Safety Officer
  Food and Drug Administration
  Center for Biologics Evaluation and Research
  Office of Compliance and Biologics Quality
  Division of Inspections and Surveillance
  Bioresearch Monitoring Branch
IND Overview

• IND Overview
  > What is an IND?
  > When is an IND required?
  > How does the IND impact clinical trial management?

• IDE Overview
  > What is an IDE?
  > Responsibilities under an IDE
  > Challenges & Potential Compliance Issues
    • Recommendations for mitigating

What is an IND?

• The **Investigational New Drug (IND) Application** is a formal notification by the study sponsor to the FDA that a drug or biologic will be used in a clinical investigation. The IND Application is a summary of the investigational plan.
• The IND Application is submitted for evaluation by the FDA. The FDA responds within 30 days with issues (otherwise the IND automatically goes into effect). The FDA may:
  > Determine that the IND application cannot be accepted as submitted (changes required)
  > Notify the sponsor that the clinical investigation(s) in the IND may begin
  > Notify the applicant that the clinical investigation qualifies for an IND Exemption
• All clinical investigations involving drugs or biologics require an IND unless the investigation meets the IND Exemption criteria outlined in 21 CFR 312.2 (see slide 4)
What is an IND? (cont’d)

- Note: “IND” may refer to the IND Application or the issuance of an “IND Number” by FDA.
  > Studies are said to be conducted “Under IND” when the IND requirements apply, and may only begin after the IND becomes effective.
  > Studies are said to be “Not Under IND” when the investigation has qualified for an IND Exemption. Studies “Not Under IND” have no “IND Number”.

What is a Clinical Investigation?

- Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice. [21 CFR 312.3(b)]
21 CFR 312.2(b)(1) – Criteria for IND Exemption

- The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:
  - The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
  - If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
  - The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
  - The investigation is conducted in compliance with the requirements for institutional review set forth in 21 CFR 56 and with the requirements for informed consent set forth in 21 CFR 50; and
  - The investigation is conducted in compliance with the requirements of 21 CFR 312.7.

Who Applies for the IND?

- The individual or entity who undertakes the clinical investigation ("sponsor") is responsible applying for the IND (if required) and any ongoing reporting to the FDA required under the terms of the IND. The sponsor may be a drug company (in the case of commercial research) or an individual clinician (in the case of investigator initiated research).
  - When an individual clinician is acting as the study sponsor, he or she acts as both sponsor and investigator and assumes the regulatory responsibilities of both.
- The IRB at each site must verify that there is an IND in effect, or …
- If the investigation meets the criteria for an IND Exemption, the IRB at each site must verify that the use of the drug in the clinical investigation is consistent with the IND Exemption criteria.
Is an IND Needed? Who is Responsible for the Determination?

• The party planning to conduct a clinical investigation using a marketed drug is responsible for determining whether the planned study meets the criteria for an exemption. But…
  > On request, FDA will advise on the applicability of this part to a planned clinical investigation. 21 CFR 312.2(e)
• Unless the exemption is verified by the FDA, the IND Exemption determination must be verified by the IRB as part of its review of the investigational plan.

How Does an Investigator Determine if an IND is Required?

• Review the protocol
• Review the exemption criteria (21 CFR 312.2)
• Review the product labeling and related literature
• Does the clinical investigation meet the criteria for IND Exemption?
• If the investigation clearly does not meet the Exemption Criteria, an IND application is required. Submit a written IND application to the FDA.
• If the investigation clearly does meet the Exemption Criteria, no IND application is required. Submit for IRB approval and the IRB will verify that the investigation is IND exempt consistent with the exemption criteria outlined in 21 CFR 312.2
• If you are not sure, contact the IRB for guidance. The FDA is also available for consultation.
How Does an Investigator Determine if an IND is Required When Joining a Sponsored Clinical Investigation?

• Ask the sponsor for details of any determinations
• Request the IND Number if there is an IND

What Happens if the FDA Disagrees with a Determination of IND Exemption made by the Investigator (and verified by the IRB)?

• For example, a clinical trial was conducted without an IND and, after the investigation is completed and the results published, the FDA determines that the clinical investigation did not meet the criteria for an IND Exemption.
• Always be conservative. If there is doubt, the IRB will advise you to contact the FDA. If the FDA determines that the investigation qualifies for an exemption, they will not accept the IND application and instead will verify the exemption. This verification of Exemption is submitted to the IRB.
How does the Management of IND Trials Differ from IND Exempt Trials?

<table>
<thead>
<tr>
<th>Trials that are IND Exempt</th>
<th>Trials for Which an IND is Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject to 21 CFR 50 and 21 CFR 56 only</td>
<td>Subject to 21 CFR 312, 21 CFR 50 and 21 CFR 56</td>
</tr>
<tr>
<td>Adherence to ICH GCP is not an absolute expectation</td>
<td>The FDA expects all trials under IND to adhere to ICH GCP</td>
</tr>
<tr>
<td>Not subject to routine inspection but may be inspected in response to a problem and/or complaint</td>
<td>Subject to routine site inspection and/or inspection in response to a problem or complaint</td>
</tr>
<tr>
<td>No ongoing reporting requirements directly to FDA.</td>
<td>Ongoing reporting directly to the FDA is required (adverse events, progress reports). Direct FDA reporting is the responsibility of the individual/entity who applied for the IND.</td>
</tr>
<tr>
<td>No Form FDA 1571 or Form FDA 1572</td>
<td>Form 1571 and/or 1572 is required</td>
</tr>
</tbody>
</table>

Regardless of IND status, all investigations require IRB approval; ongoing reporting to the IRB and all investigators must adhere to IRB policy, MMC/Einstein institutional policy and 45 CFR 46.

1572

- When a clinical investigation meets the criteria for an IND Exemption, no 1571 or 1572 is required.
  > 1571: INVESTIGATIONAL NEW DRUG APPLICATION (IND)
  > 1572: STATEMENT OF INVESTIGATOR
- When there is an IND, Form 1571 is completed by the individual or entity who applies for the IND (Sponsor). This may be a drug company or local investigator. If it is a local investigator, that person is considered the study sponsor.
- When there is an IND and there are multiple sites, a 1572 is completed by each investigator. The completed 1572 must be forwarded to the Sponsor prior to each investigator’s participation in the research.
- An important purpose of the 1572 is to confirm in writing that the investigator is aware of his or her obligation to adhere to 21 CFR 312. If there is no IND, there is no legal requirement that mandates adherence to 21 CFR 312, and no need for a 1572.
Other Relevant Facts

• The FDA will not accept an IND application if the investigation meets the criteria for exemption.
• If an investigation is placebo controlled, this does not necessarily affect the IND determination. A placebo controlled investigation may be IND exempt if it otherwise meets the criteria for an exemption.
• An IND is not needed for the off-label use of a lawfully marketed drug in the practice of medicine. As defined by the FDA, off-label use in medical care is when then the primary use of the drug is to treat the patient, but not study the safety or effectiveness of the drug in a systematic way. The FDA does not regulate the practice of medicine.
• One IND number will apply to all sites involved in a clinical investigation. Sometimes one IND number will apply to multiple clinical investigations involving the same drug.

What is an IDE?

• An Investigational Device Exemption (IDE) allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data.
• Permits the device to be shipped lawfully for the purpose of conducting investigations of the device.
Examples of Medical Devices

- Surgical lasers
- Wheelchairs
- Sutures
- Pacemakers
- Vascular grafts
- Intraocular lenses
- Orthopedic pins
- Diagnostic products, including pregnancy test kits or imaging systems

Additional examples:
> FDA Information Sheet on Significant Risk and Nonsignificant Risk Medical Device Studies

Three Types of Studies described in IDE regulations at 21 CFR 812

<table>
<thead>
<tr>
<th>IDE Exempt</th>
<th>Significant Risk (SR)</th>
<th>Non-Significant Risk (NSR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not subject to IDE regulations</td>
<td>Subject to IDE Regulations (21 CFR 812)</td>
<td>Subject to IDE Regulations (21 CFR 812)</td>
</tr>
<tr>
<td>No IDE application required</td>
<td>FDA approved IDE application required (21 CFR 812)</td>
<td>No IDE application required (assumed to have an approved IDE after IRB approval 21 CFR 812)</td>
</tr>
</tbody>
</table>
When is an FDA approved IDE required?

- All clinical evaluations of investigational devices must have an approved IDE before the study is initiated unless
  > the investigation is exempt from the IDE regulations, or
  > the study involves a nonsignificant risk device as determined by the IRB

Studies Exempt from IDE Regulations

- Consumer preference testing
- Testing of a device modification
- Testing of two or more devices in commercial distribution if the testing does not collect safety or effectiveness data or put subjects at risk [21 CFR 812.2(c)(4)]
- Studies of an already cleared medical device in which the device is used/investigated in accordance with the indications in the cleared labeling [21 CFR 812.2(c)(1) & (2)]
- Some diagnostic device studies (e.g., in vitro diagnostic studies) if they comply with the labeling requirements set forth in 21 CFR 809.10(c) and if the testing complies with the criteria set forth at 21 CFR 812.2(c)(3)
Studies Subject to the IDE Regulations

• Significant Risk Device Studies \([21 \text{ CFR } 812.3(m)]\)
  1) Intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject
  2) Purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject
  3) For a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject, or
  4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

• Nonsignificant Risk Device Studies \([21 \text{ CFR } 812.3(m)]\)
  > Studies that do not meet the definition of a Significant Risk device study
Responsibilities Under the IDE Regulations

Sponsor Responsibilities

- Determine whether an IDE application is required [21 CFR 812.2(b)(1)(ii)]
- For non-exempt device studies, make the initial risk determination:
  > If Significant Risk,
    • submit an IDE application to FDA for approval
    • advise investigators about the risk status along
    • provide the IDE approval letter and number to the IRB when requested
    • submit for IRB approval including rationale used in making the risk assessment
  > If Non-Significant Risk,
    • Submit for IRB approval including rationale used in making the risk assessment
      - IRB’s NSR determination serves as the FDA’s surrogate for review, approval, and continuing review
Sponsor Responsibilities

- Selecting qualified investigators
  > Providing investigational plan and report of prior investigations
  > Obtaining investigator agreements
- Selecting qualified monitors and monitoring the study
  > Study compliance
  > Unanticipated adverse device effects
- Obtain IRB approval and if required, FDA approved IDE
- Maintain accurate and complete records
  > Correspondence and reports
  > Device shipment and disposition
  > Investigator agreements and financial disclosures
  > Adverse device effects
- Reporting to FDA, IRBs and Investigators
- Device control & labeling
- Abbreviated list of requirements under 21 CFR 812.2(b)

Investigator Responsibilities

- Conducting study in accordance with
  > Investigator agreement with sponsor
  > Investigational plan
  > IRB and FDA requirements (conditions for approval)
- Financial disclosures
- Obtaining informed consent in accordance with 21 CFR 50
- Maintain accurate and complete records
- Reporting to Sponsor and IRBs
- Supervision of the device use
- Device disposal
IRB Responsibilities

- IRB should make sure it receives sufficient information to make this determination, including, but not limited to:
  - Description of the device
  - Reports of prior investigations with the device
  - Protocol
  - Sponsor risk assessment and rationale for the risk determination
- IRB should document the risk determination
  - Meeting minutes
  - For Significant Risk devices – a copy of the FDA IDE approval or conditional approval letter
  - For Non-Significant Risk devices – FDA will issue an NSR letter upon written request
- IRB need not make the risk determination for studies that are exempt from the IDE regulations
- Ensure that requirements at 21 CFR 50 (informed consent) and 21 CFR 56 (IRB review) are satisfied

Summary...

- Who decides whether an IDE application is required?
  > Sponsor (initial determination)
  > IRB
- Who makes the SR or NSR determination?
  > Sponsor (initial determination)
  > IRB
Challenges and Potential Compliance Issues

Vignette: Is an IND Needed?

- An investigator in your department is planning a clinical investigation of Tylenol vs. Motrin for tension headache?
- Is an IND needed?
- You know that both Tylenol and Motrin are legally marketed products. What else do you need to know?
- For what purpose is the data to be used? What is the dosage/frequency? What is the population? Is IRB approval planned? How will the trial be advertised?
- Who would be responsible for determining if an IND is needed and applying for the IND if it is needed?
Vignette: Is an IND Needed?

- A large pharmaceutical company approaches an investigator in your department. The investigator is invited to participate in a Phase II investigation of a compound called GBV-221.
- Is an IND needed? What information do you need to know?
- Who would be responsible for determining if an IND is needed and applying for the IND if it is needed?

Determining Whether an IND/IDE is Necessary

- Use of approved drugs or information provided to the IRB
- Suggested approaches:
  > When in doubt contact the FDA
  > Guidance for investigators and IRB
  > Request information related to the criteria for IND/IDE in the IRB application/submission packet
  > Include criteria in the IRB reviewer’s checklist
IRB Application (or Submission Packet)

- IRB should receive:
  - Listing of all drugs, devices, biologics used in the study:
    - Commercially available?
    - If yes, within label?
    - IND/IDE number and holder
  - Status of the IND/IDE application
    - If no application has been filed, ask for justification
  - Copy of the IND/IDE correspondence

Data & Safety Monitoring

- Risk and complexity are significant determinants of the degree and method of monitoring.
  - Early studies allow for more flexibility in monitoring
    - PI performs monitoring
    - If “high risk”, committee may be required
  - Phase III studies
    - Data Safety Monitoring Board
Data & Safety Monitoring

- Shared responsibility
- FDA Guidance:
  > To determine whether risks to subjects are minimized, an IRB may appropriately request information about the approach to trial monitoring:
    - Has a DMC been established? If so:
      - What is its scope and composition?
      - How often with the DMC meet?
      - Is there a statistical basis for early termination, when relevant?

Informed Consent Pitfall

- Not requiring that information given to subjects is consistent with 21 CFR 50.25
  > e.g., possibility that FDA may inspect the records
Support for Investigators & Sponsor-Investigators

- Institutional Guidance & SOPs
- Clinical Trials Offices/Regulatory Staff
  - Prepare IND/IDE applications for investigators
  - Provide guidance and assistance to investigators and study teams
- Protocol templates
  - Incorporate institutional policies/expectations
- Forum for inter-departmental dialogue
  - Identify and address needs for guidance and tools to serve researchers and others in unified approach

Sources of Additional Information
Contacts to Find Out if the Research Needs an IND or IDE

Drugs: CDER Division of Drug Information  
888-463-6332  301-796-3400  
druginfo@fda.hhs.gov

Biologics: CBER Manufacturer’s Assistance  
800-835-4709  301-827-1800  
Industry.Biologics@fda.hhs.gov

Devices: CDRH Manufacturer’s Assistance  
800-638-2041  301-796-7100  
dsmica@fda.hhs.gov

Helpful Websites

- FDA Homepage: www.fda.gov  
  > Includes links to the Federal Register Notices, FDA guidance documents.
- Compliance Programs:  
  www.fda.gov/ora/compliance_ref/default.htm
Guidance Documents

- Drugs
  http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/default.htm
- Vaccines, Blood and Biologics
- Devices
  http://www.fda.gov/medicaldevices/deviceregulationandguidance/default.htm

Draft Guidance Documents

- Examples:
  > IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed.
  > Considerations When Transferring Clinical Investigation Oversight to Another IRB
  > Exculpatory Language in Informed Consent
  > IRB Continuing Review after Clinical Investigation Approval
  > Financial Disclosure by Clinical Investigators
IRB Information Sheets

- [http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm](http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm)
- Examples:
  - Institutional Review Boards Frequently Asked Questions
    - Information Sheet
  - Non-Local IRB Review
  - Sponsor-Investigator-IRB Interrelationship

Einstein IRB Contact Information

**East Campus Office**
- Belfer Building, Room 1002
  1300 Morris Park Avenue
  Bronx, NY 10461
- Phone: 718-430-2237
- Fax: 718-430-8817

**West Campus Office**
- 3308 Rochambeau Ave
  Bronx, NY 10467
- Phone: 718-798-0406
- Fax: 718-798-5687

Website: [http://www.einstein.yu.edu/irb](http://www.einstein.yu.edu/irb)
Includes: Policies and Procedures, Submission Guidelines, Forms, and Educational Materials
I. Investigational Drug or Biologic

A. Investigational New Drug Application (IND)
   1. Research use of an unapproved investigational drug or biologic must be done under an IND (Investigational New Drug) application process through the FDA.
   2. Current Federal law requires that a drug or biologic be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

B. Sponsor Responsibilities
   1. Sponsor-initiated protocols require the sponsor to file the IND Application with the FDA.
   2. All FDA/sponsor IND correspondence must be submitted to the CCI/IRB with the Research Application.

C. Investigator Responsibilities
   1. Investigator-initiated protocols require the PI to file an IND Application with the FDA. The IND Application and instructions are found at http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm
   2. The FDA IND application and all subsequent correspondence between the FDA and the investigator must be submitted to the CCI/IRB.
   3. Although FDA regulations permit research to begin 30 calendar days after the IND Application has been filed, the CCI/IRB will make the final determination on a case-by-case basis to assure that research subjects will not be subjected to unreasonable risk.

D. IND Exemption
   An IND exemption applies to the clinical investigation of a drug product that is lawfully marketed in the United States. In order to be exempt from the requirement for an IND, the investigator must apply for an exemption to the CCI/IRB advising that all of the following conditions have been met. As part of the protocol review, the CCI/IRB will determine the appropriateness of the exemption.
   1. The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
2. If the drug that is undergoing investigation is lawfully marketed as a prescription
drug product, the investigation is not intended to support a significant change in
the advertising for the product;
3. The investigation does not involve a route of administration or dosage level or
use in a patient population or other factor that significantly increases the risks (or
decreases the acceptability of the risks) associated with the use of the drug
product.

E. Treatment Use of An Investigational Drug
The FDA permits an investigational drug to be used for treatment use under a treatment
protocol or Treatment IND when:
1. The drug is intended to treat a serious or life-threatening disease. (See also the
Emergency Use Drug or Biologic Policy)
2. There is no comparable or satisfactory alternative drug or other therapy available
to treat that stage of the disease in the intended patient population.
3. The drug is under investigation in a controlled clinical trial under an IND in effect
for the trial, or all clinical trials have been completed, and
4. The sponsor of the controlled clinical trial is actively pursuing marketing approval
of the investigational drug with due diligence.
5. Treatment protocols require review and approval by the CCI/IRB.

II. Medical Device

B. Definition
A medical device is defined, in part, as any health care product that does not achieve its
primary intended purpose by chemical action or by being metabolized. Medical devices
also include diagnostic aids, such as reagents and test kits for *in vitro* diagnosis.

C. Investigational Device Exemption (IDE)
1. An investigational device is a medical device that is the subject of a clinical study
designed to evaluate the effectiveness and/or safety of the device. Clinical
investigations undertaken to develop safety and effectiveness data for medical
devices must be conducted according to the requirements of the IDE regulations
[21CFR part 812].
2. Unless exempt from the IDE regulations, an investigational device must be
categorized as either "significant risk" (SR) or "non-significant risk" (NSR).
3. Significant Risk studies require submission to the FDA for an IDE. The FDA IDE
application and all subsequent correspondence between the FDA and the
sponsor/investigator must be submitted to the CCI/IRB.
   1. IDE application and instructions are found at
4. NSR studies require the usual CCI/IRB review and approval with regard to
informed consent, record keeping, and study monitoring.
5. Device studies require review and approval by the CCI/IRB.
6. If an investigator proposes the initiation of a claimed NSR investigation to the CCI/IRB, and if the CCI/IRB agrees that the device study is NSR and approves the study, the investigation may begin immediately, without submission of an IDE application to FDA.
7. Any safety and efficacy data collection on a significant risk device for other than approved indication requires an IDE in advance of IRB approval.

D. Significant Risk (SR) and Non-Significant Risk (NSR) Definitions
1. An SR device study is defined as a study of a device that –
   1. presents a potential for serious risk to the health, safety, or welfare of a subject and
      1. is intended as an implant; or
      2. is used in supporting or sustaining human life; or
      3. is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or
      4. otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
2. An NSR device investigation is one that –
   1. does not meet the definition for a significant risk study.

CCI/IRB Joint Policy
Approved 5/8/03
Revised 10/20/04
Administratively revised 3/4/08