Responsibilities of Sponsor-Investigators

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Objectives

• To review the responsibilities of a Sponsor-Investigator
• To review the FDA regulations relating to INDs or IDEs
• To provide an overview of Columbia University’s IND/IDE Assistance Program

FDA Definitions

• Sponsor - an individual, company, academic institution or other organization that takes responsibility for and initiates a clinical investigation. (Not source of funding per FDA definition)
• Investigator - an individual under whose immediate direction a test article is administered or dispensed.
• Sponsor-Investigator – an individual who initiates and conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed, involving a subject.
What is an IND or IDE?

- Investigational New Drug (IND) application to the FDA is a request for authorization to administer an investigational drug or biologic to humans.
- Investigational Device Exemption (IDE) application to the FDA is a request for authorization to administer an investigational device to humans.

When is an IND needed?

- Clinical investigation with a drug.
  
  AND

- Clinical Investigation is not exempt from IND regulations.

What is an IND Exemption?

If the drug product is lawfully marketed in the US, all the exemption criteria must be met:

- Study is not intended to be reported as a well-controlled study for a new indication or significant labeling change AND
- Study is not intended to support a significant change in advertising AND
- Does not involve a route of administration, dosing level, or patient population that significantly increases the risk (or decreases the acceptability of risk) AND
- The investigation is conducted in compliance with requirements for review of an IRB and informed consent AND
- The investigation is not intended to promote or commercialize the product
Definition of Drug

• "articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease." [21 USC 321 (g)(1)(B)]; or affects the structure or function of the body (except food).
• FDA Draft Guidance Oct 2011 reviewed when an IND is not needed.
• IND Needed?
  – Non-approved drug – YES
  – Marketed drug for unapproved use – YES if does not meet exemption criteria
  – Dietary supplements – YES if intended for diagnosis, cure, etc…

Medical Devices

• A medical device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent or other similar or related article or component part or accessory which is:
  – Intended for diagnosis of disease or cure or mitigation, treatment or prevention of a disease
  – Intended to affect the structure of any function of the body
  – Achieves its primary intended purposes through physical action and not chemical or metabolic action
  – Medical devices range from dental floss to an artificial heart valve

Investigational Device Exemption (IDE)

• All clinical investigations with a device either must have an IDE or be exempt from IDE regulations.
  – Sponsor and IRB responsibilities for risk determination
    • Is the study with a significant risk device or non-significant risk device?
  – IRB serves as FDA surrogate for NSR investigations
    • If NSR, then need abbreviated IDE where IRB is responsible for initial and continuing review of the study
Responsibilities of the S-I

The S-I has the responsibilities of both a Sponsor and an Investigator; responsibilities include:

- Selecting qualified investigators
- Providing the investigators with the information they need to conduct the study properly
- Ensuring proper monitoring of the study
- Ensuring that the study is conducted in accordance with the general investigational plan and protocols
- Ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug or device
- Overall regulatory compliance with FDA regulations, institutional policies and any other requirements

Responsibilities of the S-I

- Assuring IRB review and approval
- Obtaining informed consent from subjects
- Conducting the study according to the signed FDA Form 1572 or investigator statement, protocol and applicable regulations
- Maintaining accurate case histories on each subject’s participation in the study
- Ensuring control of investigational drug/device

Regulatory Documentation
**FDA Forms For IND**

**What is FDA Form 1571?**
- The cover sheet for the Investigational New Drug Application.
- “Contract” between Sponsor and FDA.
- Should accompany the original and each subsequent amendment or report to the FDA.

**What is FDA Form 1572?**
- ‘Statement of Investigator’ to be completed by the principal investigator of each site.
- Identifies the facilities where the research will take place, the reviewing/approving IRB and sub-investigators participating in the research study.

**What is FDA Form 3674?**
- Certification that the investigator has appropriately registered the trial on ClinicalTrials.gov.

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**FDA Forms for IDE**

**Required Information in an IDE application:**
- May use FDA Form 3514 as cover sheet, but not required.
  - Name and address of sponsor
  - Report of prior investigations
  - An investigational plan that includes purpose of the study, protocol, risk analysis, description of the device and monitoring procedures
  - An example of the investigator agreement to be signed by the investigators and a list of the names and addresses of all investigators
  - Certification that the S-I and all sub-investigators have signed the investigator agreement
  - IRB information and IRB approval when available
  - Copies of all labeling for the device
  - Copies of all informed consent forms to be utilized
  - Any other relevant information that FDA requests for review of the IDE application.

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**Regulatory Documentation: IRB**

- Assure IRB review and approval
- Keep all IRB correspondence
  - Initial review
  - Renewals
  - Amendments
  - Unanticipated Problem (UP) reports
  - Other IRB correspondence
Selection of Qualified Investigators

- It is the sponsor’s responsibility to select qualified investigators.
- Select investigators qualified by training and experience.
- Required documents for each investigator include:
  - Signed FDA Form 1572 or Investigator Agreement
  - Curriculum Vitae
  - Financial disclosures

Provide Information to Other Investigators

- The S-I must inform other investigators about the investigational product, such as safety information or new observations.
- For multicenter studies, the S-I should have a plan to distribute updated information to site investigators about the product.
1. Failure to ensure proper monitoring of the clinical investigations [21 CFR 312.50 and 312.56(a)].

According to study records, subjects were enrolled in Protocol (b)(4) between February 20, 2007 and September 8, 2008. Our inspection found that you did not monitor any aspect of the study. As the sponsor of Protocol (b)(4) conducted under Investigational New Drug Application (IND) (b)(4), you were responsible for ensuring that this study was adequately monitored for compliance with regulatory requirements, thereby ensuring the data quality, and that the rights, safety, and welfare of study subjects were adequately protected. (See 21 CFR 312.56 (requiring sponsors to monitor the progress of the investigation, and to take specific steps if such monitoring reveals noncompliance with the study Investigator agreement, the investigational plan, or FDA regulations, as well as to address developing safety information.)

Monitoring

The act of overseeing the progress of a clinical trial, and ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirement(s).
WHAT’S THE DIFFERENCE?

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<th>Inspection</th>
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<tr>
<td>WHO?</td>
<td>Sponsor</td>
<td>Industry Sponsor, IRB, Funding Organization</td>
<td>Regulatory Agency</td>
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<tr>
<td>WHAT?</td>
<td>Protection, Safety and Data Accuracy</td>
<td>Protection, Safety and Data Accuracy</td>
<td>Safety, Integrity of the Data</td>
</tr>
<tr>
<td>WHY?</td>
<td>Bringing a trial to Compliance</td>
<td>Ensures Compliance</td>
<td>Asses Compliance</td>
</tr>
<tr>
<td>WHEN?</td>
<td>Continuously</td>
<td>During, After</td>
<td>During, After</td>
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SPONSOR RESPONSIBILITIES

Monitoring
- Subject Safety.
- Data Quality & Integrity.
- Determine risks of the study.
- Timely assessment of AEs.
- Adjust the intervention accordingly.
- Review and evaluate drug/device safety and effectiveness.
- Compliance with federal, local and institutional requirements.

(ICH 5.18.3) 21CFR312.3(c), 21CFR812.40

Special Reporting Requirements for IND
IND Protocol Amendments

- Protocol amendments must be sent to the FDA.
- S-I must submit to FDA before implementation.
- IRB approval is needed prior to implementation.
- Protocol amendments include:
  - A new protocol
  - Safety or design-related changes to an existing protocol
  - New investigator (notification is required within 30 days of being added)

IND Information Amendments

- Information amendments must be sent to the FDA. These include:
  - New toxicology, chemistry, manufacturing, control (CMC) or other technical information
  - Notice of discontinuance of a clinical study
  - Others, not within the scope of protocol amendments, safety reports or annual reports.

IND Safety Reports

(effective 3/25/11)
IND Safety Reporting
• Required Safety Reporting for Sponsors of INDs.
  – Focuses on the most significant adverse reactions
  – Suspected Adverse Reaction (SAR) - evidence that the investigational product may be the cause of a safety problem. Examples include:
    • A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
    • One or more occurrences of an event that is NOT commonly associated drug exposure, but is otherwise uncommon in the population exposed to the drug
    • An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

IND Safety Reports: Timelines
• 7-day (calendar) report
  – Notify FDA via phone, email or fax of any fatal or life-threatening suspected adverse reaction (SAR)
• 15-day (calendar) report
  – Serious, unexpected, suspected adverse reaction (SAR)
  – Serious suspected adverse reactions (SAR) that occur at a rate higher than expected
  – The S-I is also responsible to report any findings from studies that are not conducted under his/her IND such as:
    • Any findings from laboratory animals or in vitro testing that suggests a significant risk for human subjects.
    • Any findings from epidemiological studies, pooled analysis of multiple studies or clinical studies that suggest a significant risk to study participants.
    • Serious adverse events from bioavailability and bioequivalence studies.

IND Safety Reporting
• The investigator OR sponsor is responsible for determining that an adverse event or suspected adverse event is “serious” or “life-threatening.”
• The sponsor is responsible for:
  – Determining whether the adverse event is “unexpected” for reporting purposes.
  – Identifying all IND safety reports previously submitted to FDA concerning a similar SAR, and analyzing the significance of the suspected adverse reaction in light of previous information.
  – Notifying FDA and all participating investigators of new safety information as soon as possible, but no later than 15 calendar days after the sponsor determines that the information qualifies for reporting.
Special Reporting Requirements for IDE

Device Regulations
The S-I must get prior approval from the FDA under an IDE for any changes to the protocol which affect safety to human subjects or the overall design of the study or device.

<table>
<thead>
<tr>
<th>Changes that Require Prior Approval by the FDA before Implementation</th>
<th>Changes that Do Not Require Prior Approval before Implementation (S-I must notify the FDA in writing within 5 working days.)</th>
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</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Emergency changes</td>
</tr>
<tr>
<td>Type or nature of study control</td>
<td>Non-significant design changes to the device</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Secondary endpoint</td>
</tr>
<tr>
<td>Statistical methods for evaluation</td>
<td>Changes to the name of the device</td>
</tr>
<tr>
<td>Significant design changes to the device</td>
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<tr>
<td>Expansion of the study</td>
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<td>Sample size changes</td>
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<td>Early termination</td>
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IDE Reports to the FDA (21 CFR 812.150)

<table>
<thead>
<tr>
<th>Event</th>
<th>FDA</th>
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<tbody>
<tr>
<td>Unanticipated Adverse Device Effect (UADE)</td>
<td>Within 10 working days</td>
</tr>
<tr>
<td>Withdrawal from FDA/IRB approval</td>
<td>Within 5 working days</td>
</tr>
<tr>
<td>Investigator List</td>
<td>Every 6 months</td>
</tr>
<tr>
<td>Progress report</td>
<td>Annually</td>
</tr>
<tr>
<td>Deviations from the investigational plan</td>
<td>Needs pre-approval or within 5 working days</td>
</tr>
<tr>
<td>Informed consent violation</td>
<td>Within 5 working days</td>
</tr>
<tr>
<td>Recall and device disposition</td>
<td>Within 30 working days</td>
</tr>
<tr>
<td>Significant risk determination (If an IRB determines that a device is a significant risk device, and the sponsor had proposed that the IRB consider the device not to be a significant risk device, the sponsor shall submit to FDA a report of the IRB’s determination within 5 working days)</td>
<td>Within 5 working days</td>
</tr>
<tr>
<td>Final report</td>
<td>Within 30 working days (notification of completion or termination of study) and 6 month report</td>
</tr>
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</table>
Register the Trial on www.ClinicalTrials.gov

Trial Registration on ClinicalTrials.gov

- FDA Form 3674: Certification that the Sponsor has appropriately registered the trial on www.ClinicalTrials.gov.
- According to Section 801 of the Food and Drug Administration Amendments Act (FDAAA801) (Public Law 110-85, Title VIII), all principal/sponsor investigators are required to register their research in ClinicalTrials.gov and provide the results for all:
  - Phase II to IV interventional studies
  - Studies involving drugs, biological products and medical devices regulated by the FDA
- *Excluded studies include Phase I drug trials, small feasibility/pilot studies of devices and non-interventional (observational) clinical research.

Trial Registration on ClinicalTrials.gov (continued)

- In general, the Responsible Party for an applicable clinical trial must submit required information 21 days after the first patient is enrolled.
- What are the required data elements?
  - Study summary
  - Recruitment information (inclusion/exclusion criteria)
  - Location
  - Contact and administrative information
- Penalties for responsible parties who fail to register applicable clinical trials are significant and may include civil monetary penalties and, for federally-funded trials, the withholding or recovery of grant funds.
FDA Inspections

• The S-I must ensure his/her research is “audit ready” at all times.
• FDA inspections of records and reports:
  – Permit FDA inspections of records and reports related to the investigation upon request.
  – Provide copies of records and reports upon written request.
  – In 2011, the number of FDA Form 483s issued was over 10,000.

Significant Observations from FDA Inspections

For clinical investigators:
• the most frequently cited violation was noncompliance with the protocol
• Failure to maintain accurate case histories
• Lack of supervision of research personnel
• consent documentation
• IRB approval and reporting
• Drug/device accountability
CU IND/IDE Assistance Program

- Collaboration with the IRB
- Assistance for Sponsor-Investigator trials
  - Understanding obligations
  - Preparing/submitting application
  - Protocol preparation
  - Reporting to FDA
  - Monitoring plans
  - FDA Inspections

- Consultative services – best to consult with service early in the process
- Provide education and guidance to investigators regarding the regulatory responsibilities as the sponsors of INDs or IDEs
  - New sponsor-investigators (S-I): in-person training
- Active collaboration with IRB: new approvals and renewals require training completion and submission of annual/progress reports.
CU IND/IDE Assistance Program

- Provide guidance in the preparation and submission of sponsor-investigator IND or IDE requirements
  - What documents are needed to file?
  - Instructions for initial application, and all correspondences with FDA
  - How often? What other regulatory requirements?
- Annual/Progress reports, amendments/supplements, safety reports

Thank You