



# **Ensuring the Safety of Clinical Trials (Investigations)**

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# Outline

- I. Purpose of this Presentation
- II. A Brief Review of the Clinical Investigator Responsibilities in Clinical Investigations
  - Adverse Event Reporting
  - Role of a DSMB
  - Institutional Review Boards
- III. Means of Oversight of a Clinical Investigation
- IV. Helpful Hints for Conducting a Quality Clinical Investigation
- V. Pertinent References

# Purpose of Presentation

- To make clinical investigators aware of important responsibilities to adequately conduct clinical investigations
  - Importance of collecting and reporting **quality data**
  - Importance of adhering to U.S. regulatory requirements and to **GCPs**
- This knowledge is important to ensure:
  - Results of an investigation are reliable and valid
  - Rights, safety and welfare of human subjects are protected
  - Investigation is conducted in compliance with regulatory requirements

## Purpose of Presentation (continued)

### To understand, collect and report Quality Data

Data that are **A**tributable, **L**egible, **C**ontemporaneous, **O**riginal, **A**ccurate (ALCOA), complete, and current

### To understand and conduct a Quality Investigation

- An investigation that has quality data
- Conducted in accordance with the IRB approved protocol
- Conducted in accordance with all applicable regulatory requirements

**Quality Investigations lead to Quality Data**

# Purpose of Presentation (continued)

## Understand what Good Clinical Practice (GCP) is...

- Principles/guidelines for conducting a clinical investigation
- Ethical and scientific quality standards for designing, conducting, performing, monitoring, auditing, recording, analyzing and reporting clinical investigations\*
- International Conference on Harmonization - E6 Good Clinical Practice Guideline
- GCP is also defined by FDA regulations under 21 CFR 312.120

\*<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf>



# Why Conduct Clinical Investigations as per Applicable Regulatory Requirements?

- To provide greater assurance that the conduct of the investigation meets acceptable standards and guidelines
- To provide greater assurance of data quality and human subject protection in clinical studies
- To reduce the likelihood of encountering significant non-compliance, data-discrepancy issues, and regulatory actions
- To enhance data reliability and acceptability upon which regulatory approval decisions are made

# When Clinical Trials are not Conducted as per Applicable Regulatory Requirements

- FDA can reject data from that clinical site and/or the entire marketing application
- Subjects in clinical investigations are exposed to unnecessary risks and hardships
- FDA can take regulatory action against the clinical investigator, e.g., issue WL or disqualify the Clinical Investigator



# A Note About Sponsor-Investigator

An individual who both initiates and conducts a clinical investigation

**Dual Role**



**Dual Responsibilities**

# Sponsor

- A person who takes responsibility for and initiates a clinical investigation
- May be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization
- The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator

# Investigator Responsibilities

- Protecting the rights, safety and welfare of subjects in the clinical investigation
- Conducting the clinical investigation according to signed statement of investigator (Form 1572), investigational plan and applicable regulations





# STATEMENT OF INVESTIGATOR (Form FDA-1572)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
FOOD AND DRUG ADMINISTRATION

**STATEMENT OF INVESTIGATOR**  
*(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)*  
(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014.  
Expiration Date: May 31, 2009.  
*See OMB Statement on Reverse.*

**NOTE:** No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR

[Large light blue rectangular area for entering name and address of investigator]

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED.

CURRICULUM VITAE

OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL

# Statement of Investigator

## Form FDA-1572 includes:

- Name and address of the clinical investigator
- Name and code number of any protocol(s)
- Name and address of research facility(ies) and any clinical labs
- Name and address of the responsible IRB
- Names of sub-investigators
- **Signed commitment by the investigator**

# Statement of Investigator (continued)

## A Signed Commitment by the Investigator to:

- Conduct the investigation according to the protocol, and make changes only after notifying sponsor, except to protect the safety, welfare and rights of subjects
- Personally conduct or supervise the investigation
- Inform subjects that the test product is being used for investigational purposes and ensure requirements for informed consent and IRB review and approval are met
- Read and understand the Investigator's Brochure, including potential risks and side effects of the drug
- Report to the sponsor adverse experiences that occur during the investigation



# Investigator Safety Reports

- **Required** to submit all reports to the sponsor of the investigation. The sponsor is required under 312.33 to submit Annual Reports on the progress of the clinical investigation.
- Safety Reports:
  - **Required** to immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and **must** include an assessment of whether there is a reasonable possibility that the drug caused the event.
  - Study endpoints that are serious adverse events (e.g., all-cause mortality) **must** be reported in accordance with the protocol **unless** there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the investigator **must** immediately report the event to the sponsor.
  - The investigator **must** record non-serious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol.
- Final Report:
  - An investigator shall provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation.
- **Required** to report to the IRB all unanticipated problems involving risks to human subjects or others.

# Sponsor's IND Safety Reports

- Adverse Event (AE or Adverse Experience) = Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related
- Sponsors and Sponsor-Investigators are **required** to submit written IND Safety Reports to FDA and all participating clinical investigators
- IND Safety Reports are submitted on FDA Form 3500A, electronic, or narrative format
- Sponsor must report as soon as possible but **no later than 15 calendar days** any potential serious risks from clinical trials, or other sources from the use of the test product including any:
  - ✓ **Serious and unexpected suspected adverse reaction**
  - ✓ **Findings from other studies that suggest a significant risk in humans exposed to the drug**
  - ✓ **Findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug**
  - ✓ **Increased rate of occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure**
- Sponsors are to submit reports of any **unexpected fatal or life threatening suspected adverse reaction associated with use of the drug** by telephone or facsimile as soon as possible but **no later than 7 calendar days** after the initial receipt of the information

# Statement of Investigator (continued)

## A Signed Commitment by the Investigator to:

- Assure that those assisting in the trial are informed of their obligations in meeting these commitments
- Maintain adequate and accurate records
- Obtain initial and continuing review and approval from an IRB that is in compliance with the regulatory requirements listed under 21 CFR Part 56
- Promptly report to the IRB all changes in the research and all unanticipated problems involving risk to subjects or others
- Not make changes in the research without IRB approval except to eliminate immediate hazards to human subjects
- Comply with all other regulatory requirements regarding obligations of a clinical investigator

# Investigator Responsibilities (continued)

- Obtain IRB approval prior to enrolling any subjects
- Obtain and document informed consent signed and dated by subject or legally authorized representative (LAR)
- Follow the study protocol and investigational plan
- Ensure that changes to the protocol are reported to the sponsor and approved by the IRB prior to initiating the change

# Investigator Responsibilities (continued)

- Control the investigational products
- Use test products only in/on subjects enrolled in the clinical investigation
- Ensure adverse effects/events (AEs) are appropriately documented and reported
- Maintain adequate clinical investigational records and reports
- Ensure that all investigational records and reports are available for FDA inspection



# Means of Oversight of a Clinical Investigation

- Investigator's study oversight and supervision
- IRB's initial and continuing reviews
- Sponsor/CRO monitoring and audits
- Audits by US and International Regulatory Agencies
- Adjudication Review Committees
- Data Safety Monitoring Board (DSMB)



# Regulatory Monitoring vs. DSMB

**DSMB = Data Safety Monitoring Board,  
which performs clinical monitoring of an  
ongoing investigation**

**Please Note:**

**Regulatory Monitoring  $\neq$  Clinical Monitoring**

# Data Safety Monitoring Board

- A group that periodically reviews and evaluates accumulated data from a clinical investigation for:
  - Subject safety
  - Study conduct and progress, and
  - As necessary, efficacy
- They make recommendations to the sponsor regarding the continuation, modification, or termination of the trial

# Reminder for **Personnel** Involved in a **Clinical Investigation**

- Keep ALL files organized at all times
- Keep all source documents and study related materials
- Keep ALL correspondence:
  - Sponsor, IRB, monitors, study subject letters, faxes, e-mails, memos and phone contacts
- Know your IRB's requirements
- Know the sponsor's/IRB's adverse event reporting requirements
- Know the protocol:
  - Inclusion/exclusion criteria, study windows, study procedures
- Know each study staff member's roles and responsibilities:
  - **The clinical investigator is ultimately responsible**

# Reminder for **Personnel** Involved in a **Clinical Investigation** (cont.)

- Sponsor responsibilities may be transferred to a Contract Research Organization (CRO)
- CRO assumes the regulatory responsibility and obligations for transferred tasks that are specified in writing
- Responsibilities that are not contracted in writing will remain the obligation of the sponsor
- Keep all test article accountability records current, complete and accurate:
  - Shipping receipts, enrollment logs, dispensing logs
- Written procedures are recommended:
  - SOPs, Quality Policy, Training procedures, Job descriptions, etc.
- Have a Preventive and Corrective Action Plan if problems arise

# Conclusion

- It is important to capture the highest quality data possible to ensure that the investigational product
- is reasonably safe
- is reasonably effective



# Pertinent References



# REGULATIONS (All Products)

- 21 CFR 50: Protection of Human Subjects
- 21 CFR 54: Financial Disclosure
- 21 CFR 56: Institutional Review Boards
- 21 CFR 58: Good Laboratory Practice for Non-Clinical laboratory Studies

# REGULATIONS (Drugs and Biologics)

- 21 CFR 312: Investigational New Drug Application (IND)
- 21 CFR 314: New Drug Application (NDA)
- 21 CFR 316: Orphan Drugs
- 21 CFR 320: Bioavailability and Bioequivalence Requirements
- 21 CFR 601: Biological Licensing (BLA)

# For More Information

- FDA Home Page  
[www.fda.gov](http://www.fda.gov)
- FDA Good Clinical Practices  
<http://www.fda.gov/oc/gcp/default.htm>
- Code of Federal Regulations (CFR)  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm>
- Center for Drug Evaluation and Research (CDER) Office of Scientific Investigations (OSI)  
<http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm090085.htm>
- Center for Biologics Evaluation and Research (CBER) Division of Inspections and Surveillance  
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/ProductSurveillance/default.htm>
- Center for Devices and Radiological Health (CDRH) Bioresearch Monitoring (BiMo)  
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/BioresearchMonitoring/default.htm>



# Thank You

**For questions contact:**

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