University Hospitals Case Medical Center

## Investigator Responsibilities in FDA Regulated Research

**Joseph Gibbons, M.D.**
Assistant Professor of Medicine
Hematology/Oncology
Case Western Reserve University School of Medicine
Chair, University Hospitals Case Medical Center IRB

## Disclosure

- Site visitor for Association for the Accreditation of Human Research Protection Programs (AAHRPP)



## Investigator Responsibilities in FDA Regulated Research

- Why this subject?
- FDA Guidance on Investigator Responsibilities
- Recent Noncompliance Letters

Deitz, Robert, M.D.
Sunday, May 23, 2010
7:55 PM
**1. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].**

Inserted from
<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm208002.htm>



b. Protocol **(b)(4)** Section 10.1.1 (Pharmacokinetics) required samples to be drawn on Day 1 at pre-dose, and at 15 minutes, 30 minutes, 45 minutes, 1 hour, and 2 hours after study drug infusion was **initiated**. The following subjects' pharmacokinetic (PK) samples were drawn at the incorrect time intervals. Specifically, the samples were collected after the **completion** of the infusion rather than after the **initiation** of the infusion:

| Protocol-specified PK sampling schedule (post infusion initiation) | PK sampling time according to protocol (2400 hours) | Actual time of PK sampling (2400 hours) |
|---|---|---|
| **Subject 002 Day 1 Study Drug Infusion Time: 1330-1405** | **Subject 002 Day 1 Study Drug Infusion Time: 1330-1405** | **Subject 002 Day 1 Study Drug Infusion Time: 1330-1405** |
| Just prior to dose | Just prior to dose | 1325 |
| 15 minutes (post infusion initiation) | 1345 | 1420 |
| 30 minutes (post infusion initiation) | 1400 | 1435 |
| 45 minutes (post infusion initiation) | 1415 | 1450 |
| 1 hour (post infusion initiation) | 1430 | 1505 |
| 2 hours (post infusion initiation) | | |



## The Bad Apples

## Research Misconduct

"Research misconduct does not include honest errors or honest differences of opinion"

- From S. Woollen, Associate Director for Bioresearch Monitoring, FDA, 2003

If FDA has information indicating an investigator has *repeatedly or deliberately failed to comply* with the requirements identified in the Code of Federal Regulations or has submitted false information to FDA or a sponsor s/he may be disqualified and be subject to criminal and civil liability.



## Differences between the role of clinician and role of researcher

| Clinical Care | Research |
|---|---|
| • Individualized | • Rigid, pre-determined |
| • Physician-driven | • Protocol driven |
| • Patient welfare | • Knowledge, validity |
| • Established standards | • Protocol elements |



## Role of FDA

- Protect the safety of people
- Guidance for drug development
  - Investigational New Drug (IND) (November 1995)
  - Exploratory IND (January 2006)
  - Manufacturing
  - Preclinical Toxicology
  - Clinical Trial Monitoring
  - Adverse Event Regulations
  - Clinical Trial Endpoints for the approval cancer drugs and biologics (May 2007)

## Roles and Responsibilities Investigator

**Investigator** means an individual who actually conducts a clinical investigation. In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team.

*21 CFR 312.3 (b)*



## Key Definitions

Investigational New Drug
- A drug or biologic drug used in a clinical investigation

Investigational Device
- A device that is the object of an investigation

Sponsor
- An individual, company, institution or organization that takes responsibility for the initiation, management and/or financing of a clinical investigation

Sponsor – Investigator
- An individual who both initiates and conducts the investigation
- The responsibilities of a sponsor-investigator include both those of the sponsor and investigator



## Key Definitions (continued)

Investigational New Drug Application (IND)
- A request for authorization from the FDA to administer an investigational drug or biologic to humans

Investigational Device Exemption (IDE)
- Allows the investigational device to be used in a clinical study to collect safety and effectiveness data required to support a Premarket approval or a Premarket notification to the FDA

## When is an IND required?

Sponsor/Investigator intends to conduct the study with an investigational new drug

or

Sponsor/Investigator intends to conduct the study with an approved drug, but in a new indication, dose form or dose range that is not covered in the current labeling



## You're In Charge: Principal Investigator




## You're In Charge: Investigator Responsibilities

**It sounds really boring, but it can keep you in your job and out of jail.**

## An Investigator is responsible for

- Ensuring that an investigation is conducted according to
  - Signed investigator statement (FDA 1572)
  - Study protocol
  - IRB requirements
  - All applicable federal, state, & institutional regulations
- Control of all drugs/agents/devices under investigation
- For protecting the rights, safety, and welfare of subjects under the investigator's care

Reference: Guidance for Industry Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects (U.S. Department of Health and Human Services Food and Drug Administration, October 2009)
http://www.fda.gov/downloads/drugs/guidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf



## Investigator Responsibilities

- Respond to participants who have an adverse event
- Keep participant fully informed of any new information
- Protect the privacy of participants and maintain confidentiality of data
- Either obtain consent or designate authorized person to obtain consent
- Provide reports as required by the sponsor and the IRB
- Make records available for inspection
- Ensure accountability of investigational drugs, devices or biologics
- Provide contact information on consent form
- Provide a data and safety monitoring plan

Source: UHCMC IRB Policy: Investigator Responsibilities



## Investigator Responsibilities – Investigational Device Exemption (IDE) Holders

IDE holders have additional responsibilities

- Understanding when an IDE is required
- Obtaining an IDE
- Annual reporting
- Complying with all federal (21 CFR 812) and institutioanal policies

## Qualifications for Investigators

- Qualified by education, training, & experience to assume proper conduct of the trial
- Aware of & comply with GCP
- Familiar with the use of investigational product(s)
- Interested in the scientific aspects of the trial



## Qualifications for Investigators

- Have adequate time to:
  - Discuss, read & approve protocol
  - Identify & recruit subjects
  - Properly assess & follow subjects
- Have adequate personnel & resources to conduct the trial
- Able to meet the recruitment targets
- Conduct the trial in compliance with the protocol without deviation



## Qualifications for Investigators

- Maintain a list of research team members to whom trial-related duties have been delegated
- Keep research team members well informed about the trial at all times
- Permit monitoring, auditing & inspection by sponsors & regulatory authorities

## Control of Investigational Drug/Agent/Device

- An investigator shall **distribute** the drug/agent/device **only to subjects under** the investigator's personal **supervision** or under the supervision of a sub-investigator responsible to the investigator
- The investigator shall not supply the investigational drug/agent/device to any person not authorized by the investigator to receive it.



## Investigator Reports

### Progress Reports

- Sending reports to the sponsor as required by the protocol.
- Sponsor-investigators are required under 312.33 to submit annual reports to FDA on the progress of the clinical investigation.

### Safety Reports

- Promptly report to the sponsor any adverse effect that may reasonable be regarded as caused by, or probably cause by, the drug/agent/device.
- Sponsor-investigators are required to report adverse effects that are both serious and unexpected and/or deaths directly to FDA in accordance with 312.32



## Investigator Reports

### Final Report

- Provide the sponsor/FDA (for sponsor-investigators) with an adequate report shortly after completion of the investigation.

### Financial Disclosure Reports

- Provide sponsor with sufficient accurate and current financial information to allow for accurate certification/disclosure as required under part 54.

## Investigator Reports

### New information

- New information available during the course of the trial must be passed along to the IRB
- If the new information is relevant to the subject's participation, consent form must be updated & approved by the IRB
- For subjects already on study, provide the new information at their next visit or sooner if there is a risk to the patient or if consent is likely to be revoked
- Current subjects should be "re-consented" with the new IRB-approved consent form
- Delay accrual until IRB approval of new information



## Investigator Reports

### Adverse Event/Safety reporting

- Adverse Event (AE): any untoward medical occurrence in a trial subject, which does not necessarily have a causal relationship with the study treatment
- Adverse Drug Reaction (ADR): any noxious and unintended response to an investigational pharmaceutical product
- There is a causal relationship between the adverse event and the pharmaceutical product
- Unexpected ADR: any adverse reaction, the nature or severity of which is not consistent with product information (such as in the I.B.)



## Investigator Reports
## Adverse Event/Safety Reporting

### Serious Adverse Event (SAE):

- Any untoward medical occurrence that meets one or more of the following:
  - Results in death
  - Is life-threatening
  - Requires inpatient hospitalization or prolongation of an existing hospitalization
  - Is a congenital anomaly or birth defect
  - Is a medically significant event, for any reason, these might include pregnancy, cancer, overdose, etc.

## Investigator Reports
## Adverse Event/Safety Reporting

### Questions to ask

- Is the event "unexpected"?
- Is it reported in the Investigator's Brochure?
- Is it a known events that has become more frequent or severe?

NCI Expedited reporting guidelines: http://ctep.cancer.gov/forms/NCI_AEReporting_Gdln_final.pdf



## Investigator Reports
## Adverse Event/Safety Reporting

### Questions to ask

- Is the event treatment-related?
  - Reasonable causal relationship to be determined based upon prior experience with treatment
  - If an association cannot be ruled out, then it should be considered to have a reasonable relationship
  - Not-related, unlikely, possible, probable, definite

NCI Expedited reporting guidelines: http://ctep.cancer.gov/forms/NCI_AEReporting_Gdln_final.pdf



## Investigator Responsibility Overview

- For drugs, biologics, and devices:
  - Ensure study is conducted according to the signed investigator statement or agreement, the investigational plan and regulations
  - Protect the rights, safety and welfare of subjects
  - Control of test materials

## Supervision

- Federal regulations require investigators supervise drug and device investigations
- Delegation is common and expected
  - Investigator must provide "adequate" supervision
  - Investigator is accountable for regulatory violations resulting from failure to "adequately supervise"



## Supervision

- FDA focuses on 4 major issues of supervision
  - Delegated staff were qualified to perform tasks
  - Staff received adequate training
  - Adequate supervision and involvement in ongoing study
  - Adequate supervision and oversight of 3rd parties as reasonably possible



## Factors that impact Investigator's ability to provide adequate supervision

## Form FDA 1572



## Form FDA 1572

- Statement signed by the investigator
- Provide information to the sponsor
- Assure the investigator will comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug or biologic



## When is Form FDA 1572 Required?

- Under the regulations, a 1572 is required for studies of investigational drugs or biologics conducted under an Investigational New Drug (IND) application
- A 1572 is not required for studies not conducted under an IND and is not applicable to investigational device studies

## When an Investigator Signs the 1572 – What do you commit to?

- Following the protocol
- Telling participants the investigation is research
- Reporting adverse events
- Understanding the Investigational Brochure
- Informing all support personnel of the investigation requirements
- Maintaining adequate records
- Complying with IRB policies

(continued)

Information Sheet Guidance for Sponsors, Clinical Investigator, and IRBs – Frequently Asked Questions – Statement of Investigator (Form FDA 1572). Final May 2010



## When an Investigator Signs the 1572 – What do you commit to?

- Reporting study changes and unanticipated risks to the IRB
- Not making changes in the research without IRB approval
- Complying with the requirements regarding the obligations of clinical investigators
- Personally supervising or conducting the investigation

Information Sheet Guidance for Sponsors, Clinical Investigator, and IRBs – Frequently Asked Questions – Statement of Investigator (Form FDA 1572). Final May 2010



## Protecting Subjects

- Protocol violations that present unreasonable risks
  - Failure to follow protocol MAY be considered a failure to protect the rights, safety and welfare of subjects
  - For example: Failure to comply with inc/exc criteria may enter a subject that the product may cause increased risks

## Protecting Subjects (continued)

- Failure to perform safety assessments that are to detect toxicity may be a failure to protect subjects
- Compliance with protocol is best way to minimize these risks

## What are the common violations cited by the FDA?

- Informed consent
- Investigator responsibilities
- Protocol deviations
- Study records
- IRB approval
- Regulatory documentation



## You're In Charge

**Running a clinical trial can be complex**

- You will need full support from your research team
- You will need to be careful and stringent on every trial-related issue
- You will need to protect the rights and integrity of your trial subjects
- You will need to supervise the investigation

## What does it mean to personally supervise or conduct the investigation?



## Understanding what "Personally Supervise" really means

- Appropriate delegation
- Adequate training
- Adequate supervision

FDA guidance for industry: Investigator responsibilities - protecting the rights, safety and welfare of study subjects - 2009



## What is appropriate delegation?

Qualified by:
- Education
- Training
- Experience
- Licensure (when required)

to perform the delegated task

Most clinical/medical tasks require formal medical training/licensing/certification

## What is adequate training?

- Familiarity with purpose of the study and protocol
- Understanding of the specific details of the protocol and investigational product to perform assigned tasks
- Knowledge of regulatory requirements and acceptable standards for conducting clinical trials and the protection of particpants



## What is adequate supervision?

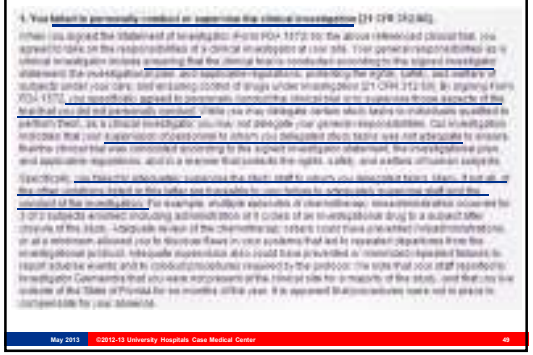
- Level of supervision should be appropriate to staff, nature of the trial and participant population.



## Holland Case
## Lax Supervision

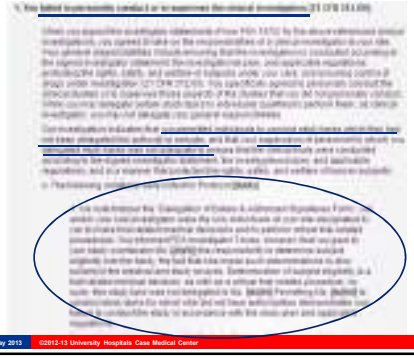
- Study coordinator enrolled ineligible subjects in oncology trials
- Coordinator altered source records and created fraudulent CRFs to make subjects appear eligible
- Data manipulations should have been apparent to attentive clinician
- Subject who was ineligible due to poor renal and liver function was enrolled, dosed, and died as a result
- Study coordinator sentence to 71 months in prison and debarred from many future involvement in FDA regulated research
- Dr. Holland – 5 years probation, $500k restitution to defrauded drug companies, disqualified

## FDA PI Warning Letter 2/16/11





## FDA PI Warning Letter 2/2/09





How do you manage delegation, training and supervision?

## Tools to manage delegation, training and supervision - documenting

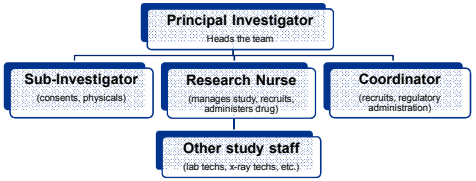
- Maintain a list of study staff and what study-specific tasks have been delegated
  - Describe the delegated tasks
  - Identify qualifying training
  - Identify dates of involvement in the study



## Tools for managing

Create an organization chart

- Identify study team members including specific job responsibilities
- Review responsibilities and determine review intervals






## Sample study specific task list

| Study Task | Specific Actions | Individual Responsible |
|---|---|---|
| Screening | Telephone screening of interested participants | RC |
| | Complete screening checklist | RN/RC |
| Eligibility | Initial review with potential participant | RN/Sub-I |
| | Final eligibility | PI |
| Consent | Obtain informed consent | RN/Sub-I |
| Clinical Procedures | Draw blood | RN |
| | Complete history/physical exam | PI/Sub-I |
| Data management | Complete case report forms | RN/RC |
| | Data entry | RC |
| | Document study activities in medical record | PI/RN |
| | Review of source documents | RN/RC |
| | Monitor/review of AEs | PI |

## Sample staff signature and delegation of responsibility log



## Examples of inappropriate delegation of study-related tasks

- Assessment of inclusion/exclusion criteria by individuals with inadequate medical training
- Physical examination performed by unqualified personnel
- Evaluation of adverse events by individuals lacking appropriate medical training or knowledge of the clinical protocol or study agent
- Informed consent obtained by individuals who lack the training and knowledge of the protocol need to discuss risks and benefits of study



## Elements of a supervisory plan:

- Routine meetings with staff and sponsor's monitors
- Procedure for timely correction and documentation of identified problems
- Procedures for:
  - Documenting review of performance of delegated tasks
  - Ensuring informed consent is being done appropriately.
  - Ensuring that source data are accurate

## Key Messages

- Clinical investigators play a critical role in ensuring high quality studies
- Good care of patients is not the same as Good Clinical Practices (GCP) in research
  - It is important have a clear understanding of responsibilities under FDA regulations
- At stake is public confidence and participation in the clinical trials and ultimately the availability of safe and effective products



## U. S. Food and Drug Administration

5600 Fishers Lane, Rockville MD 20857-0001
1-888-INFO-FDA (1-888-463-6332)
**Drug Information Number: 301-827-4570 (8:00 AM - 4:30 PM)**
**http://www.fda.gov/cder/guidance/index.htm**