



PEDIATRIC RESEARCH TRAINING: PI RESPONSIBILITIES

Carlton D. Dampier, MD, CPI

Medical Director, OCR

Assistant Dean for Clinical Research

Professor of Pediatrics-Division of Hematology, Oncology, and BMT

404-778-2561

cdampie@emory.edu

INVESTIGATOR RESPONSIBILITIES

Regulatory
Agencies
(OHRP, FDA)

Institution
(primarily IRB)

Research
Subject

Sponsor

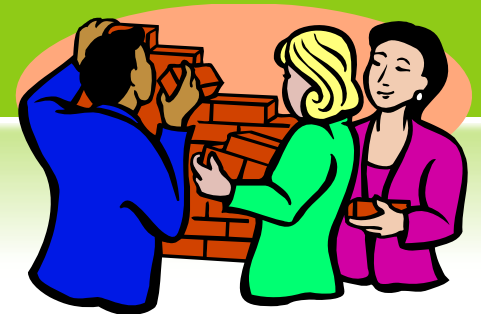
Research and Clinical Care
Teams



OVERVIEW OF INVESTIGATOR RESPONSIBILITIES

- ◎ Various sections of the Code of Federal Regulations (CFR)
- ◎ FDA October 2009 Guidance for Industry Protecting the Rights, Safety, and Welfare of Study Subjects – Investigator Responsibilities www.fda.gov
- ◎ Good Clinical Practice-The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) www.ich.org

INVESTIGATOR RESPONSIBILITIES



- ◎ Clinical research and clinical trials is a team sport
- ◎ Everyone has a responsibility for patient safety and study conduct
- ◎ Expect equality of functioning
- ◎ Expect equality of communication



OVERVIEW OF INVESTIGATOR RESPONSIBILITIES

- ◎ In conducting clinical investigations of drugs, including biological products, under 21 CFR part 312 and of medical devices under 21 CFR part 812, the investigator is responsible:
 - ◎ ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs, including biological products, or agreement for clinical investigations of medical devices, the investigational plan, and applicable regulations;
 - ◎ protecting the rights, safety, and welfare of subjects under the investigator's care
 - ◎ the control of drugs, biological products, and devices under investigation (21 CFR 312.60, 21 CFR 812.100)

INVESTIGATOR RESPONSIBILITIES PER THE FDA 1572 FOR FDA-REGULATED STUDIES

9. COMMITMENTS:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

**INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:**



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

WARNING LETTER

CERTIFIED MAIL RETURN RECEIPT REQUESTED

Sant P. Chawla, M.D.
Sarcoma Oncology Center
2811 Wilshire Boulevard, Suite 414
Santa Monica, CA 90403

Ref: 10-HFD-45-03-02

Dear Dr. Chawla:

Between August 5 and 27, 2009, Ms. Diane Van Leeuwen, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigations:

- Protocol (b)(4), entitled "(b)(4)" of the investigational drug (b)(4), performed for (b)(4).; and
- Protocol (b)(4), entitled "(b)(4)," of the investigational drug (b)(4), performed for (b)(4).

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report, the documents submitted with that report, and your September 14, 2009 written response, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Ms. Van Leeuwen presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

Regarding Protocol (b)(4):

1. You failed to conduct the studies or ensure they were conducted according to the investigational plans [21 CFR 312.60].

a. Protocol (b)(4), Section 7.4.1 (Dose Escalation and Modification) specified study drug dosages to be administered based on assigned cohort. Subject 008 was assigned to Cohort 4, with a study drug dose specification of 150 mg/m². For Cycle 4, Day 1 on September 3, 2008, the subject's height and weight were recorded as 5'0" and 132 lbs., respectively. The subject's body surface area was documented as 1.59 m², and the dose was inaccurately calculated and recorded as 274.5 mg. The correct dosage should have been calculated as 238.5 mg [150 mg/m² x 1.59 m²]. The subject's chemotherapy flow sheet documents that the subject received 274.5 mg of study drug on September 3, 2008. The administration of this miscalculated dose unnecessarily exposed the subject to an overdose, with the potential for increased adverse events.

In your September 14, 2009, written response, you indicated that the subject's chart was reviewed with the study nurses

INVESTIGATOR RESPONSIBILITY ISSUES

- ◎ Study supervision
- ◎ Delegation of study tasks/responsibilities
- ◎ Protocol adherence



INVESTIGATOR RESPONSIBILITIES-SUPERVISION

- ◎ It is common practice for investigators to delegate certain study-related tasks
- ◎ Investigator is responsible for providing adequate supervision of those to whom tasks are delegated
- ◎ Investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study
- ◎ The investigator should have a detailed plan for the supervision and oversight of a clinical trial.



WHAT IS ADEQUATE SUPERVISION OF THE CONDUCT OF AN ONGOING CLINICAL TRIAL?

- ⊙ A plan for the supervision and oversight of a clinical trial:
 - ⊙ Routine meetings with staff to review trial progress and update staff on any changes to the protocol or other procedures
 - ⊙ Procedures for ensuring study staff comply with the protocol, adverse event assessment and reporting, and other medical issues that arise during the course of the study.
 - ⊙ A procedure for ensuring that information in source documents is accurately captured on the Case Report Forms





WHAT IS ADEQUATE SUPERVISION OF THE CONDUCT OF AN ONGOING CLINICAL TRIAL?

- ⊙ A plan for quality oversight of a clinical trial:
 - ⊙ A procedure for ensuring that the consent process is being conducted in accordance with 21 CFR Part 50 and that study subjects understand the nature of their participation, risks, etc.
 - ⊙ A procedure for documenting the performance of delegated tasks in a satisfactory manner and, where appropriate, verifying findings
 - ⊙ A procedure for correcting problems identified by study personnel, outside monitors or auditors, or other parties involved in the conduct of a study

INVESTIGATOR RESPONSIBILITIES-DELEGATION

- ⦿ FDA has identified instances in which study tasks have been delegated to individuals lacking appropriate qualifications.
- ⦿ Examples of inappropriate delegation include:
 - ⦿ Screening evaluations, including obtaining medical histories and assessment of inclusion/exclusion criteria, conducted by individuals with inadequate medical training (e.g., a medical assistant)
 - ⦿ Physical examinations performed by unqualified personnel
 - ⦿ Evaluation of adverse events by individuals lacking appropriate medical training, knowledge of the clinical protocol, and knowledge of the investigational product
 - ⦿ Assessments of primary study endpoints (e.g., tumor response, global assessment scales) by individuals lacking appropriate medical training and knowledge of the protocol
 - ⦿ Informed consent obtained by individuals who lack the medical training, knowledge of the clinical protocol, or familiarity of the investigational product needed to be able to discuss the risks and benefits of a clinical trial with prospective subjects

INVESTIGATOR RESPONSIBILITIES-PROTOCOL ADHERENCE

- ⦿ There are occasions when a failure to adhere to the protocol may be considered a failure to protect the rights, safety, and welfare of subjects. Investigators should seek to minimize such risks by adhering closely to the study protocol
- ⦿ Failure to adhere to inclusion/exclusion criteria that are specifically intended to exclude subjects for whom the study drug or device poses unreasonable risks
- ⦿ Failure to perform safety assessments intended to detect drug toxicity within protocol-specified time frames
- ⦿ Significant deviations are reportable events to the IRB

OTHER INVESTIGATOR RESPONSIBILITIES

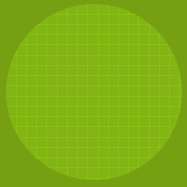
- ◎ Sponsor responsibilities for those studies where PI is also the study sponsor
 - ◎ IND or IDE holder
 - ◎ Company may be supplying device or drug but not conducting the study
- ◎ Additional reporting to FDA
- ◎ Appropriate monitoring of study site performance

OTHER INVESTIGATOR RESPONSIBILITIES

- ◎ Registration and subsequent study result data for FDA-regulated clinical trials in clinicaltrials.gov
- ◎ submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.
- ◎ Other institutional requirements
 - ◎ Financial conflict of interest reporting
 - ◎ Effort reporting
 - ◎ Financial management



No matter what happens, it is the investigator that is ultimately responsible.



QUESTIONS

