

Principal Investigator Responsibilities: Focusing on the FDA Guidance

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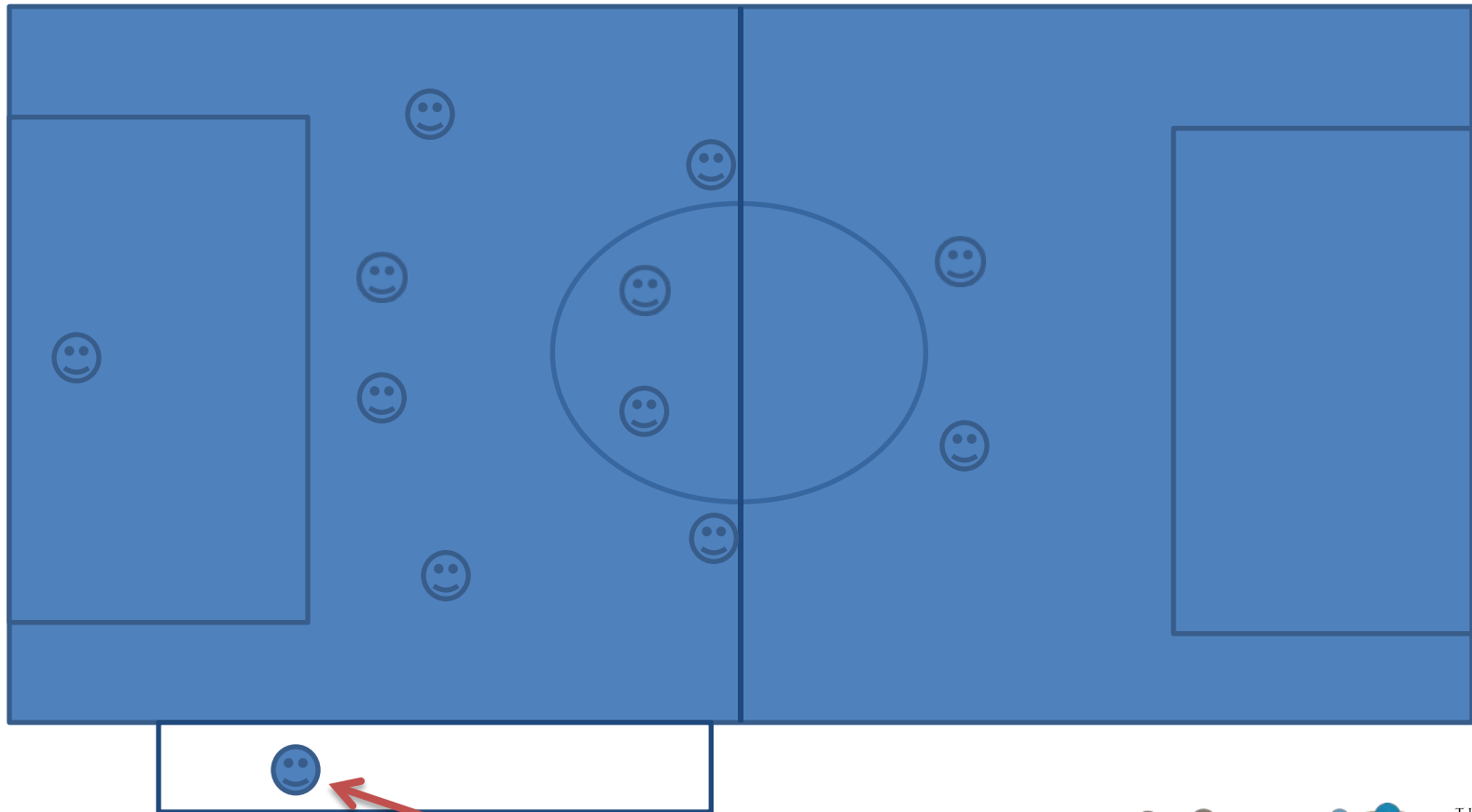
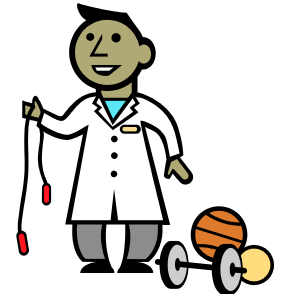


July 2012

To Cover

- Overview of the Regulations
- FDA guidance
- Key references

PI Role in a Clinical Study



Principal Investigator

Who is the PI?

- A person responsible for the conduct of the research at a study site. If a study is conducted by a team of individuals at a site, the investigator is the responsible leader of the team and may be called the principal investigator.

Study Lifecycle



Responsibilities of the PI are before, during and after a study is completed!

Who is responsible for high quality research?

Academic institution

Study Coordinator

Sponsor-investigator

Vendor

**CONTRACT
RESEARCH
ORGANIZATION**

Regulators **Bioequivalence
study**

Study Subject

Clinical Investigator

Contract Laboratory

Study nurse

SPONSOR

Sub-investigator

GLP Facility

Institutional Review Board

Which entities are directly regulated and inspected by FDA?

Sponsor-investigator

Bioequivalence study

Clinical Investigator

SPONSOR

GLP Facility **Institutional Review Board**

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Principal Investigator Responsibilities

In protecting the rights and safeguarding the welfare of people involved in research, at a minimum PIs are expected to:

- Understand and comply with ethical principles
- Understand and comply with federal regulations
- Understand and comply with NIH/FDA policies and procedures
- Understand the mandate of IRB and work effectively with them
- **Understand and comply with CNMC/CRI policies and procedures**

Principal Investigator Responsibilities

- Trial registry
- Subject Selection
- Inform consent
- Data Collection and Verification
- Adequate infrastructure to conduct the study
- Implementation and documentation of your study
- Confidentiality
- Safety Monitoring/Reporting
- Publication and reporting (i.e. clinicaltrials.gov)

Regulatory framework

- Federal Food, Drug, and Cosmetic Act (FD&C Act)
- Good Clinical Practice (GCP) Guidance
- Code of Federal Regulations (CFR) 21CFR312 and 21CFR812
- FDA Guidance
- FDA Form 1572

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
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

Procedural
October 2009

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf>

FDA Guidance

- Drafted in 2007
- Final form Issued in October 2009
- Intended to clarify FDA expectations with regard to investigator's responsibility
 - ✓ To protect the rights, safety, and welfare of study subjects
 - ✓ To conduct and supervise a clinical study in which some study tasks are delegated
 - ✓ To control drugs, biologics and devices under investigation

Two main points:

- A. SUPERVISION OF THE CONDUCT OF A CLINICAL INVESTIGATION**

- B. PROTECTING THE RIGHTS, SAFETY, AND WELFARE OF STUDY SUBJECTS**

A. SUPERVISION OF THE CONDUCT OF A CLINICAL INVESTIGATION

FDA focuses on four major areas:

- Qualifications
- Training
- Supervision of study staff
- Supervision of third parties

1. Delegation of study-related tasks:

“It is common practice for investigators to delegate certain study related tasks. When this occurs, the PI is responsible for providing adequate supervision and the PI is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the study.”

1. Delegation of study-related tasks:

- Ensure that individual is qualified by education, training, and experience
- Qualified physician should be responsible for all trial related medical decisions and care

1. Delegation of study-related tasks:

Examples of tasks delegated to individuals lacking appropriate qualifications:

- Screening evaluations (medical evaluations and assessment of inclusion/exclusion criteria)
- Physical examinations
- Evaluations of adverse events
- Assessment of primary endpoints
- Obtaining informed consent

Key points about Delegation

- Always follow the protocol!
- Always maintain a list of persons to whom significant trial-related duties have been delegated, including **type of task, training of the individual and date of involvement** . Keep one list per study!

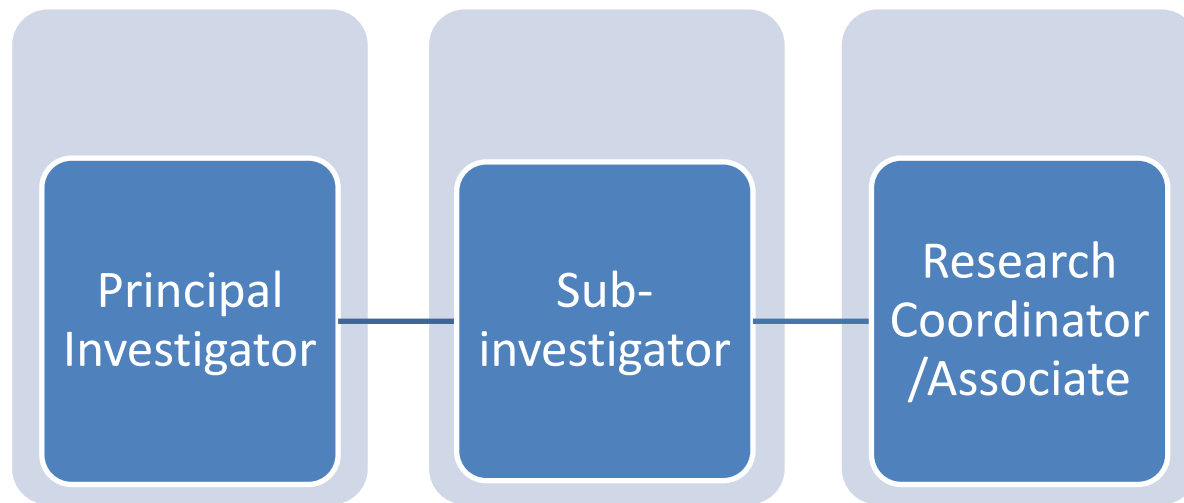
2. Adequate Training:

The PI should ensure that there is adequate training for all staff participating in the study.

PI needs to ensure:

- Familiarity with purpose of study and protocol
- Understanding of specific details of the protocol and attributes of the investigational product
- Awareness of regulatory requirements and standards for the conduct of the study and the protection of human subjects
- Competency and training of staff
- Inform any changes during the study and additional training if needed
- **Communication, communication, communication!**

3. Adequate Supervision:



PI can't delegate the primary supervisory responsibility to anybody!

3. Adequate Supervision:

- Develop a plan for the supervision and oversight of the study at the site. Supervise even highly qualified and experienced individuals.
- Plan should include:
 - Routine staff meetings: trial progress, AEs, protocol updates
 - Routine meetings with sponsor's monitors
 - A procedure for timely correction and documentation of any issues identified by monitors or auditors
 - Documentation/review the performance of delegated tasks

3. Adequate Supervision (continuation):

- Procedure for ensuring consent process
- Procedure for ensuring source data is accurate, contemporaneous, and original
- Procedure for ensuring that information from source document is accurately captured on CRFs
- Procedure for dealing with queries and discrepancies
- Procedure for ensuring study staff compliance with protocol and AE assessment/reporting requirements
- Procedure for addressing medical and ethical issues

4. Oversight of Other Parties

- a. Study staff Not in the direct employ of the PI:
PI is responsible for supervising the study tasks performed by the site study staff, even if they are not in his/her direct employees.

- b. Other parties:
 - Central lab facility reporting to sponsor
Sponsor responsibility
 - Outside Lab/Testing facility reporting to the PI
PI responsibility

B. PROTECTING THE RIGHTS, SAFETY, AND WELFARE OF STUDY SUBJECTS

- Provide reasonable medical care for study participants
- Provide reasonable access to needed medical care, either by investigator or other qualified individual (e.g., PI unavailability, or specialized care needed)
- Adhere to the protocol!

1. Reasonable Medical Care:

- For any adverse events including clinically significant abnormal laboratory values related to the trial participation
- Subjects should receive appropriate medical evaluation and treatment until resolution of any emergent condition related to the study intervention, even if the follow-up period extends beyond the end of the study.
- Inform subject when medical care is needed for conditions unrelated to the study intervention.

2. Reasonable Access to Medical Care:

- PI should be available to subjects during the conduct of the trial for medical care related to participation in the study.
- Depending on investigational product toxicity or abuse potential.
- In advance, PIs need to consider whether they can be available to the extent needed by the study.
- Delegate responsibility of medical care to specific qualified physician readily available to subjects during periods of PI unavailability.

3. Protocol Violations:

- In some cases, failure to comply with the protocol may be considered a failure to protect rights, safety and welfare of subjects because of the potential exposure to unreasonable risks.
- For example: Not adhering to inclusion/exclusion criteria before subject enrollment; or not performing protocol specific safety lab assessments.
- Adhere closely to the study protocol!

The FDA 1572 Form

<p>DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION</p> <p>STATEMENT OF INVESTIGATOR <i>(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)</i> (See instructions on reverse side.)</p>	<p>Form Approved: OMB No. 0910-0014. Expiration Date: May 31, 2009. See <i>OMB Statement on Reverse</i>.</p> <p>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)).</p>
<p>1. NAME AND ADDRESS OF INVESTIGATOR</p>	
<p>2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED.</p> <p style="text-align: center;"> <input type="checkbox"/> CURRICULUM VITAE <input type="checkbox"/> OTHER STATEMENT OF QUALIFICATIONS </p>	
<p>3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED</p>	
<p>4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.</p>	
<p>5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE</p>	
<p>6. NAMES OF THE SUBINVESTIGATORS (e.g., research fellows, residents, associates) WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).</p>	
<p>7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.</p>	

Investigator Commitments on the 1572 Form

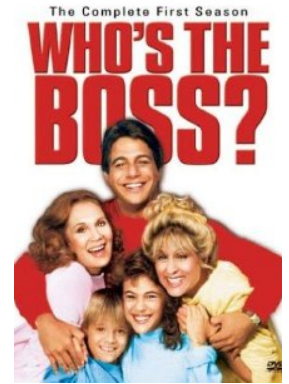
- Personally conduct or supervise investigation
- Follow protocol
- Ensure all persons assisting in study are informed of obligations
- Inform subjects that drugs are being used for investigational purposes
- Ensure informed consent (21 CFR Part 50) and IRB review, approval and reporting (21 CFR Part 56)
- Report to sponsor adverse events (21 CFR 312.64)
- Maintain adequate and accurate records and make them available for inspection in accordance with 21 CFR 312.68
- Ensure initial and continuing review by an IRB and report all changes to research and unanticipated problems involving risks to subjects, not make any changes without IRB approval except where necessary to eliminate immediate hazards
- Comply with other requirements in 21 CFR 312

Investigator Initiated Research



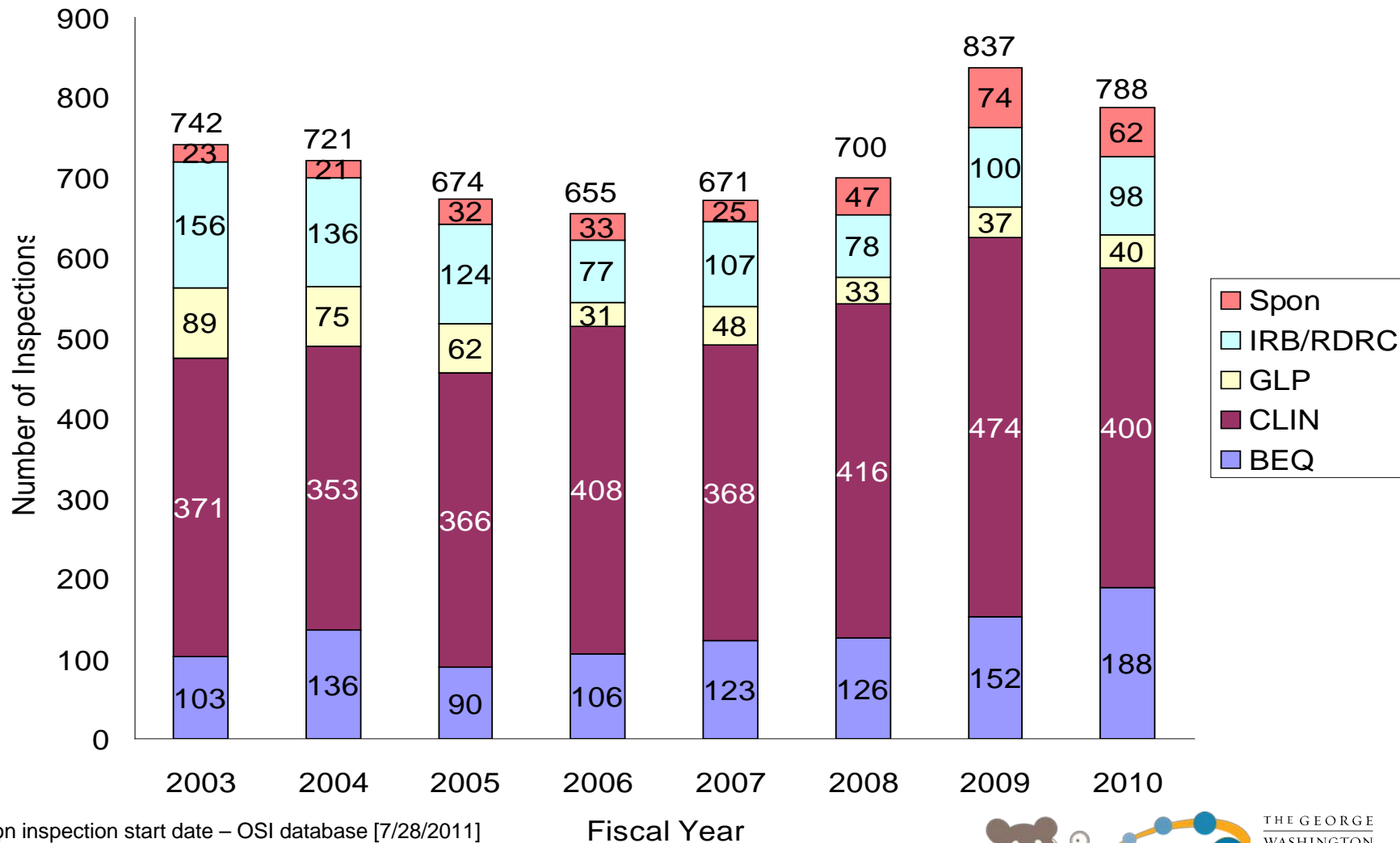
- An individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed.
- The term does not include any person other than an individual.
- The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

So...



- Clinical investigators are in charge **and** held accountable
 - FDA regulations permit sponsors to delegate their responsibilities to Contract Research Organizations (CROs) but do **not** permit clinical investigators to delegate their general responsibilities to CROs or site management organizations, subinvestigators, or study staff
- **Possible Penalties** for noncompliance
 - Warning Letters
 - Disqualifications, Restrictions and/or Debarments
 - Criminal prosecutions, prison and/or fines

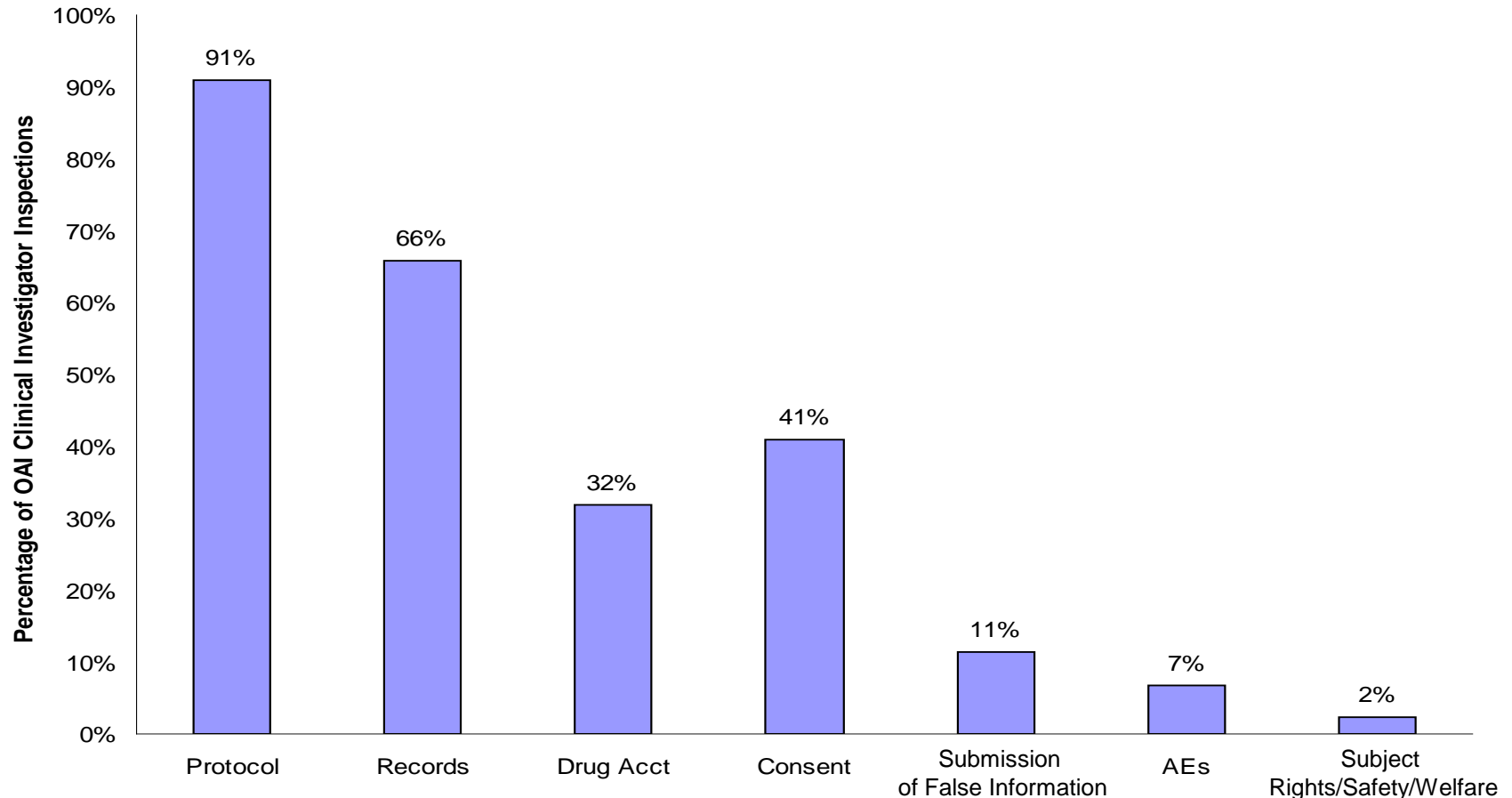
Bioresearch Monitoring Program Inspections* (CDER, FY 2003-2010)



*Based on inspection start date – OSI database [7/28/2011]

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Extracted from the FDA clinical investigator training course 2011

Frequency of Clinical Investigator Related Deficiencies Based on Post-Inspectional Correspondence Issued: OAI* Final Class (CDER, FY2010)**



*OAI: Denotes Official Action Indicated (significant deficiencies found)


**Based on letter issue date; Inspections may have multiple deficiencies, Includes OAI untitled letters, [7/28/2011]

Extracted from the FDA clinical investigator training course 2011

Common Mistakes – Risks factors

- Poor supervision and training
- Lack of investigator involvement
- Inappropriate delegation of study tasks
- Failure to adequately protect study subjects
- Overworked investigator and/or study staff

Example of FDA inspection results

 DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville, MD 20857

**NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS
AND OPPORTUNITY TO EXPLAIN (NIDPOE)**

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

[REDACTED]
[REDACTED]
[REDACTED] 20857
Springfield, Illinois 62701

Dear [REDACTED]

Between July 24, 2007 and September 11, 2007, Mr. Joel Martinez, representing the Food and Drug Administration (FDA), conducted an investigation and met with you and your staff, to review your conduct of a clinical investigation of the following protocols:

- Protocol (b) (4) : (b) (4)
[REDACTED]
performed for (b) (4)
- Protocol (b) (4) : (b) (4)
[REDACTED] performed for
(b) (4)
- Protocol (b) (4) : (b) (4)
[REDACTED]
performed for (b) (4)

1. You repeatedly or deliberately submitted false information to the sponsor in a required report [21 CFR 312.70(a)].

Our investigation found that for Protocol AI-700-33 and Protocol (b) (4), physical examinations were conducted on study subjects and medical orders/progress notes were entered with your signature while you were out of town. You admitted that you did not have access to a virtual private network (VPN) that would allow you remote access to study records for signature. This was confirmed by an email from Dr. (b) (6), Associate Chief of Staff of Research and Development, (b) (4). Specifically,

Protocol AI-700-33

- a. An American Airlines (AA) passenger itinerary obtained at your site, documented your flight from San Antonio to Dallas and then to your final destination of San Juan, Puerto Rico on 9/7/05 at approximately 7:40 am. The itinerary further showed your return flight to San Antonio occurred on 9/10/05 at approximately 7:09 pm. However,
 - i. Source documents for Subject 49-055 indicate through your signature that you performed a discharge physical exam on 9/8/05 and performed the 72-hour follow-up physical exam on 9/9/05. An (b) (4) computerized patient recording system (CPRS) documented that progress notes were written and entered into the CPRS on 9/7/05 at 15:58 (3:58 pm) and were electronically signed by you on 9/7/05 at 15:59 (3:59 pm).
 - ii. The (b) (4) CPRS documented that progress notes were written for Subject 49-057 on 9/8/05 and were electronically signed by you on 9/8/05 at 15:51 (3:51 pm).

- b. An AA passenger itinerary documented your flight AA 1049 from San Antonio, TX to Dallas, TX on 1/10/06 at approximately 2:35 pm and on to Los Angeles, CA. You then returned to San Antonio on 1/11/06.
 - i. The (b) (4) CPRS documented that progress notes were written for Subject 49-084 stating, "He tolerated the procedures well. A physical exam and safety labs were collected prior to discharge from the research clinic." This progress note was electronically signed by you on 1/10/06 at 15:23 (3:23 pm).
 - ii. The (b) (4) CPRS medical record documented that progress notes were written for Subject 49-085 and entered into CPRS on 1/10/06 using your code and electronically signed by you at 15:24 (3:24 pm).
- c. A hotel receipt from Fiesta Americana Guadalajara documented your stay in the hotel from 3/31/05 through 4/3/05. However, medical orders from CPRS for Subject 49-026 indicated that you electronically signed these orders on 4/1/05 at 11:08 am.

Protocol (b) (4)

- d. A Chicago Marriott Downtown guest folio indicated that you arrived on 10/19/03 at 13:53 (1:53 pm) and departed on 10/20/03 at 10:05 am. However, a CPRS Medical Order Details record documented for Subject 158011, a "New Order entered by [REDACTED] (PHYSICIAN)" on 10/20/03, 10:52 am, and electronically signed by you at 10:53 am.
- e. An AA passenger receipt documented your flight from San Antonio, TX to Dallas, TX and then to Guadalajara, Mexico on 9/25/03. The AA passenger receipt further shows your return flight to San Antonio, TX on 9/28/03. However, a CPRS Medical Order Details record documented for Subject 158012 that new orders were entered on 9/26/03 by you and that you electronically signed the orders on 9/26/03 at 16:14, (4:14 pm).

Final remarks

- Always conduct ethical clinical research
- Always protect research subjects
- Always generate high quality data
- Always follow the 1572
- Always create a strong communication and systems between PI, Sub-I, Study Coordinators, Pharmacy, etc.
- Always document!

If it is not documented it did not happen!

Key References

Reference	URL
FDA Guidance for Industry – Investigator Responsibilities	http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf
FDA Code of Federal Regulations (21CFR312) Investigational New Drug Application - Responsibility of Sponsor and Investigators	http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312&showFR=1&subpartNode=21:5.0.1.1.3.4 (Drugs)
FDA Code of Federal Regulations (21CFR812) Medical Devices - Responsibilities of Investigators	http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=812&showFR=1&subpartNode=21:8.0.1.1.9.5 (Devices)