

Clinical and Translational
Science Institute / **CTSI**
at the University of California, San Francisco



Welcome to Online Training for
Clinical Research Coordinators

ROLE OF THE RESEARCH COORDINATOR FDA INSPECTIONS-PREPARING for an Audit



Clinical and Translational Science Institute / CTSI
Accelerating Research to Improve Health

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UCSF

Objectives

- Overview of the FDA (Food and Drug Administration) oversight of drug development
- How are FDA inspections are conducted
- How to prepare for an FDA inspection
- How to respond to a Form 483 or Establishment Inspection Report (EIR)
- What is a Corrective Action Plan (CAP) and how to write this plan



Originally founded in 1906, currently this Agency of the Department of Health and Human Services has oversight of the following products used by the public: Food, Drugs, Medical Devices, Vaccines, Cosmetics, and Tobacco Products.

FDA Mission Statement

- To increase the years of healthy life by protecting and promoting public health and increasing access to life-saving and life-enhancing medical treatments and devices.
- To reduce the number of deaths and injuries associated with the quality and unsafe use of FDA regulated medical products.



FDA Increased Regulatory Powers

After commercial drug events occurred, harming the public in 2004, a study of the FDA was initiated through the Institute of Medicine (IOM). The IOM Report in 2006 found major deficiencies in the current FDA system for ensuring the safety of drugs on the market.

Although the **inspection of drugs in development** was in place, the authors of this IOM report called for:

- Increased regulatory powers
- Increased federal funding to support the FDA mission

Today more than ever, audits and oversight of clinical trials by either the sponsor or the FDA demands training and preparation of research personnel.



FDA Office of Regulatory Affairs (ORA)

The FDA ORA is concerned with the following actions:

- Inspections, Compliance, Enforcement, and Criminal Investigations, and
- Bioresearch Monitoring Program (BIMO) associated with clinical trials



FDA Bioresearch Monitoring Program (BIMO)

What types of activities are controlled by BIMO?

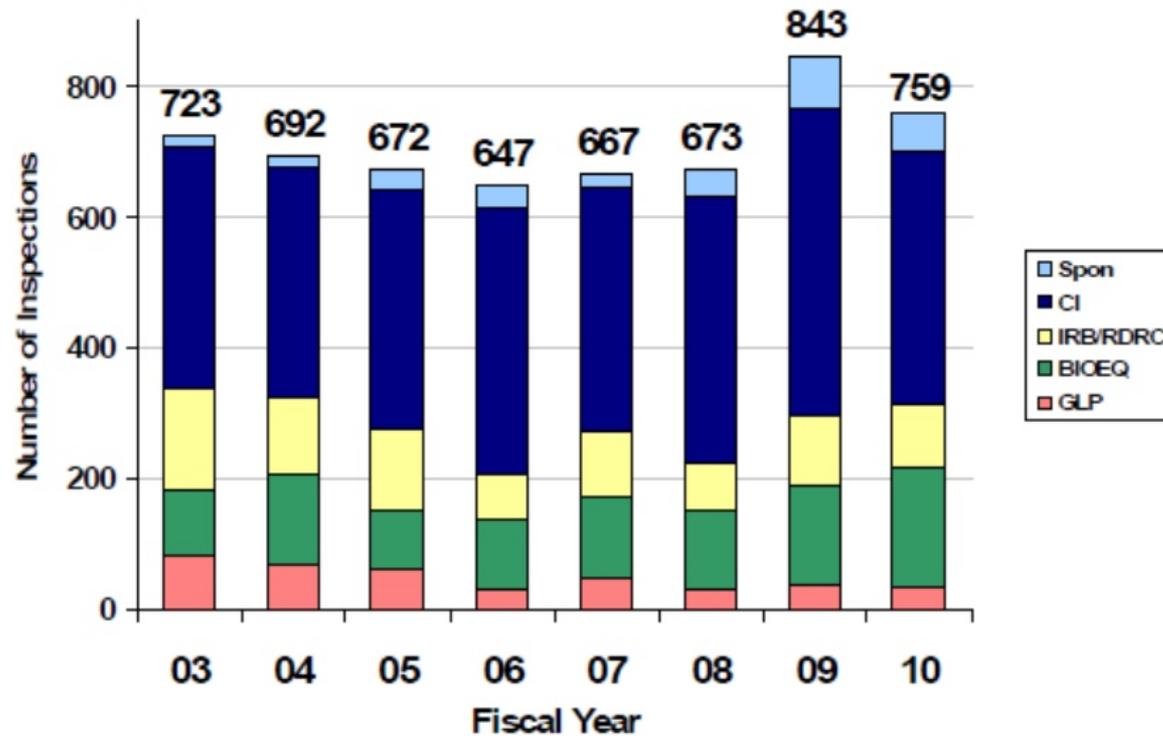
1. Inspections of investigators, sponsors, laboratories, and Institutional Review Boards (IRB).
2. Confirmation the trial was managed in adherence/compliance to federal regulations that are in place for the protection of human subjects.

When is an inspection likely to be scheduled?

- An application by the manufacturer for filed for an NDA: New Drug Application or PMA: Pre Market Approval for devices
- If evidence of research misconduct has been reported and this type of inspection is called “for cause”.



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



*Based on inspection start date
Preliminary data; FY10 subject to change [12/10/2010]

- Spon**= Sponsor
- CI**= Clinical Investigator
- IRB**= Institutional Review Board
- RDRC**= Radioactive Drug Research Committee Program
- BIOEQ**= Bioequivalence Review
- GLP**= Good Laboratory Practices

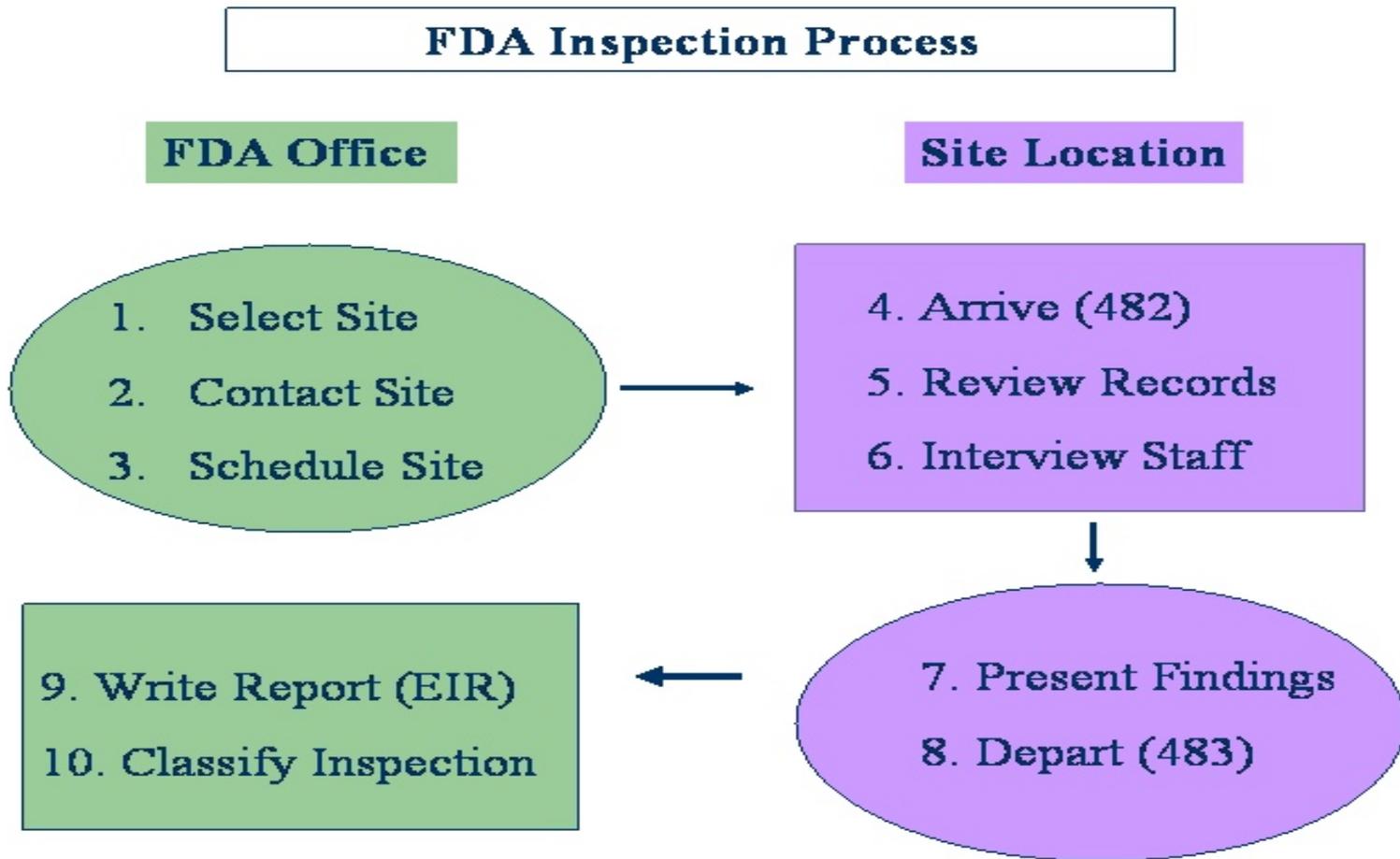


What Increases Risk for an FDA Inspection?

- Number of studies per site/PI
- Enrollment
- Time since last inspection
- Protocol Violations
- Serious Adverse Events (SAE)
- Percentage of subject deaths



What Can We Expect during a BIMO Inspection?



What Will the FDA BIMO Inspect?

Pre-approval FDA Inspections Compare:

Source Data

(Clinical Documentation of Subject –Medical records)

VS.

Case Report Forms

VS.

Data Listing Submitted for New Drug Application

(NDA)/Premarket Approval (PMA)



What Will the FDA BIMO Evaluate?

- ✓ Did subjects exist?
- ✓ Did they have the disease under study?
- ✓ Did they meet inclusion/exclusion criteria?
- ✓ Consent obtained before study participation?
- ✓ IRB review obtained?



What Does the FDA BIMO Evaluate?



- Was the protocol followed
- Did the subjects receive the assigned study drug in the dose, route and frequency specified in the protocol
- Are adverse experiences reported to the sponsor and the Institutional Review Board (UCSF CHR)
- Are the clinical medical records and documentation complete and available for inspection.
- Are the case report forms (CFR) complete and in agreement with the clinical source documentation



What Does the FDA BIMO Evaluate?

FDA Verifies PI Supervision and Oversight and Control of **all aspects of study** including:

- Investigator delegation of duties to appropriately qualified personnel
- Qualification and training of staff
- Medical care of the subject
- Day-to-day supervision and oversight: subject care, staff, execution of the protocol



FDA Inspectors Will Expect to Have Access

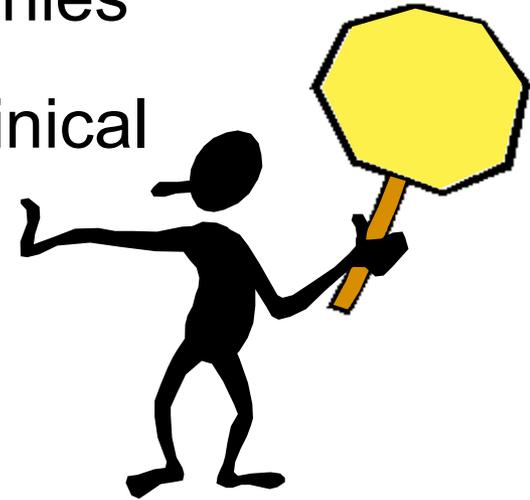
Examples of 'must have' documentation

- Study documents (investigator site file with IRB documents, study reference manual, sponsor instruction manuals for sites to conduct study , biological samples instructions etc.)
- All signed Informed Consent Documents (ICDs) including those who withdrew or did not meet eligibility to enroll
- Study Drug Records and Pharmacy SOPs for the study
- Facilities and equipment
- Site Standard Operating Procedures (SOPs)



Consequences of Failing an FDA Inspection

- Products Do Not Reach Patients
- Reputation of Investigator
 - FDA Website (Freedom of Information Act)
 - FDA Warning Letter posted for public access
- Repeat business from sponsor companies
- Suspension from conducting future Clinical Research
- Criminal prosecution



What Occurs at the End of the FDA Inspection?

- **Form FDA 483: Inspectional Observations**
Left with investigator at close of inspection

Expectation for PI: **RESPOND WITHIN 15 CALENDAR DAYS IF RESPONSE IS REQUIRED in 483 OR FDA WARNING LETTER MAY BE ISSUED!**

Establishment Inspection Report (EIR)

Prepared by FDA inspector after inspection documenting observed deficiencies and provides a full report for the FDA



483 Inspection Classifications

NAI - No Action Indicated

- Investigator and site is in compliance

VAI - Voluntary Action Indicated

- Minor deviation(s) from the regulations
- Voluntary correction requested in form of a written corrective action plan

OAI - Official Action Indicated

- Serious non-compliance requiring regulatory or administrative action by FDA; Data unacceptable



Consequences of an Official Action Indicated (OAI)

Recommendation to Reject Data and posting a Warning Letter <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/>

Disqualification of a clinical investigator (21 CFR 312.70)

- Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) letter
- FDA believes it has evidence that the clinical investigator repeatedly or deliberately violated FDA regulations governing the proper conduct of clinical studies involving investigational products or submitted false information to the sponsor. Outcome can be disqualification from receiving investigational products.

Referral for criminal prosecution to the Office of Criminal Investigations (OCI)

- Firms or individuals convicted of a felony under Federal Law for conduct relating to the development or approval of any drug product or abbreviated drug application.



How to Respond to an FDA Inspection

RESPOND WITHIN 15 CALENDAR DAYS OR FDA WARNING LETTER MAY BE ISSUED!

Preparing a Corrective Action Plan (CAP)

A corrective action plan is a written document that details the implementation of actions taken to detect and eliminate the cause of an area of non-compliance, and prevents reoccurrence of non-compliance.

How to Write a CAP?

- State the problem succinctly, including the root cause
- Break the solution into discrete measurable actions
- Identify the accountable person for each action
- Set achievable deadlines
- Monitor progress



Video – Preparing for a FDA Audit



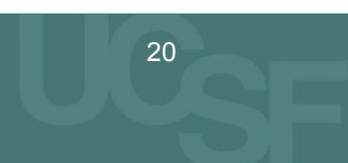
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FDA Audit Manual For Investigators

- FDA's Compliance Programs provide instructions to FDA personnel for conducting activities to evaluate industry compliance with the Federal Food, Drug, and Cosmetic Act and other laws administered by FDA.
- Compliance Programs are made available to the public under the Freedom of Information Act.

Excerpts on next three slides

[http://www.fda.gov/downloads/ICECI/EnforcementActions/
BioresearchMonitoring/ucm133773.pdf](http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/ucm133773.pdf)



- b. Compare the source documents with the CRFs and any background information provided (e.g., data tabulations provided by the sponsor) per the assignment memorandum and sampling plan (if applicable). **Determine** whether:
 - i. The study subjects met the eligibility criteria (inclusion/exclusion);
 - ii. Protocol-specified clinical laboratory testing (including EKGs, X-rays, eye exams, etc.) was documented by laboratory records;
 - iii. All adverse events were documented and appropriately reported;
 - iv. The clinical investigator assessed the severity of the adverse event and documented the relationship of the event to the test article, including any adverse event that was previously anticipated and documented by written information from the sponsor; and
 - v. All concomitant therapies and/or inter-current illnesses were documented and reported.
- c. **Determine** whether the clinical investigator reported all dropouts and the reasons to the sponsor.

G. OTHER STUDY RECORDS

Study-related information may also be recorded in other documents. **Determine** if the clinical investigator maintains other records pertinent to the study, e.g., administrative study files, correspondence files, master subject list, appointment books, sign-in logs, screening lists, and MedWatch forms. Review these records to ensure that all pertinent information has been reported to the sponsor. **Document** any discrepancies found.

H. FINANCIAL DISCLOSURE

1. Ask the clinical investigator if and when he disclosed information about his financial interests to the sponsor and/or interests of any subinvestigators, spouse(s) and dependent children.



J. TEST ARTICLE CONTROL

1. Accountability [312.62(a), 511.1(b)(7)(ii), and 812.140(a)(2)]

- a. **Determine** who is authorized to administer or dispense the test article.
- b. **Determine** whether the test article was supplied to a person not authorized to receive it.
- c. **Compare** the amount of test article shipped, received, used, and returned or destroyed. **Verify** the following:
 - i. Receipt date(s), quantity received, and the condition upon receipt;
 - ii. Date(s), subject number, and quantity dispensed; and
 - iii. Date(s) and quantity returned to sponsor. If not returned to sponsor, **describe** the disposition of the test article.
- d. **Determine** where the test article is stored, whether it was stored under appropriate conditions as specified in the study protocol, and who had access to it.
- e. If the test article is a controlled substance:
 - i. **Determine** how it is secured; and
 - ii. **Determine** who had access.

2. **Inspect** unused supplies and **verify** that the test article was appropriately labeled.

Current changes {ED: Retain "current changes" only in sections where changes made}





Data Integrity: Submission of False Information to FDA or the sponsor

Violation/Related Citation	Examples
Study records are fabricated, altered, or concealed 21 CFR 312.70; 312.62(b); 21 CFR 511.1(c); 511.1(b)(7)(ii); 21 CFR 812.119; 812.140(a)	CRFs for study subjects who did not exist or did not participate in the study
	Falsified consent documents (signatures do not match)
	Falsified records of IRB review and/or approval (human studies)
	CRFs include results about protocol-required procedures that were never done
	Specimens and/or analytical results characterized as being from a study subject that were from a different individual
False or misleading reports were prepared and/or submitted 21 CFR 312.70; 312.64; 21 CFR 511.1(c); 21 CFR 812.119, 812.150(a)	False safety data or reports are submitted
Inadequate supervision of study personnel who, in turn, fabricated, altered, or contributed false information to study records or reports 21 CFR 312.60; 21 CFR 812.100; 812.110(c)	Signatures on CRFs and/or other study documents do not match



What is the CRC Role at Inspections and Audits?

The CRC is one of the “safety nets” for the study

- Always be ‘inspection ready’
- Organize charts and consents
- Regulatory, study files up-to-date and current
- Keep current on the protocol, safety profile of the study drug(s)
- Ensure PI is involved and it is documented
- Use a checklist to prepare for an inspection or audit



UCSF Resources for the CRC

- Understand how regulatory inspections are managed and hosted at UCSF?
 - How
 - Where
 - Who supports you?
- Review the UCSF FDA Inspections Guidance Documents on HUB
<http://hub.ucsf.edu/fda-and-ohrp-inspections>
 - Site Inspection Checklist
 - Actions for a FDA Inspection
 - Facilitating FDA Inspections
- The UCSF Human Research Protection Program (HRPP) is here to help and support you!



Takeaways...



- Don't panic!
- Recognize 'regulatory agency inspection readiness' is now an 'everyday' principle
- Follow GCPs, the protocol, UCSF and departmental SOPs
- Know how to write a Corrective Action and Preventative Action (CAPA) Plan
- When in doubt – **ASK!**

