

FDA INSPECTIONS of CLINICAL TRIAL

MANAGING FDA INSPECTIONS of CLINICAL TRIALS

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Preparation for FDA Inspections

- The best preparation involves understanding the FDA inspection process
- Today's presentation will explain:
 - Why the FDA inspects clinical investigators?
 - What governs the FDA inspection process?
 - When do FDA inspections occur?
 - Who gets inspected by the FDA?
 - What FDA expects after an inspection?

FDA Provides Oversight of Clinical Trials

Why?

- To protect the rights, safety, and welfare of subjects involved in FDA-regulated clinical trials
- To verify the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications
- To assess compliance with FDA's regulations governing the conduct of clinical trials

What governs the FDA inspection of clinical trial sites?

- **Code of Federal Regulations**
 - 21 CFR 312 (Human Drugs)
 - 21 CFR 812 (Medical Devices)
 - 21 CFR 511 (Veterinary Drugs)
- **ICH-GCP**
 - The act by a regulatory authority of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or CRO facilities, or at other establishments deemed appropriate by the regulatory authority. Ref: ICH -GCP 1.29 (Inspections)

FDA Inspections

21 CFR 312 (Human Drugs)

- An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to 21 CFR 312.62.

Ref: 21 CFR 312.68

What is ICH Good Clinical Practice?

ICH

- The **I**nternational **C**onference on **H**armonization
 - The guidance was developed with consideration of the good clinical practices of EU, Japan, and US as well as those from Australia, Canada, the Nordic Countries, and WHO
- Ref: **ICH E6 GCP** 1.24- an international standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

What is the FDA Inspection Policy?

- FDA has compliance programs (CP) with written procedures within their Bioresearch Monitoring (BIMO) Program
 - Good Laboratory Practice CP 7348.808
 - **Clinical Investigator CP 7348.811**
 - Institutional Review Board CP 7348.809
 - Sponsor, CRO Monitors CP 7348.810
 - In Vivo Bioequivalence CP 7348.001

Clinical Investigator Program

- Provides for study specific inspections of physicians, veterinarians, and other investigators conducting clinical trials of human and veterinary drugs, medical devices, and biologics.

Where do FDA inspections take place?

- Inspections may be conducted anywhere in the world for studies submitted to FDA
- Inspectors may look at one study across sites or across multiple studies at one site

Who gets inspected by the FDA?

- High enrolling sites
- Sites with suspect data (no AEs, too many AEs, data not trending like other sites)
- Sites with large number of deviations
- Sites that FDA received complaints against
- Sites previously identified with compliance issues
- FDA will identify any clinical investigators whose studies were terminated, the circumstances, and whether this was promptly reported to FDA.

Inspections may be either “routine” or “directed”

- Routine
 - Inspections assigned for NDA’s
 - Assigned almost randomly on a percentage of all clinical data submitted with applications for new products.
 - An important product or crucial study key to the decision for approval
- Directed or “For Cause”(may be unannounced inspections)
 - Problems identified at IND stage
 - Complaints to FDA
 - Sponsors/monitors/CROs
 - Institutions/IRB’s
 - Subjects/whistle-blowers/public to FDA’s Division of Scientific Investigations (DSI)

When does FDA conduct GCP “BIMO” Inspections?

- FDA inspections are conducted for every NDA, usually after filing application with FDA
 - May occur at other stages based on complaints received by FDA (from whistle-blowers, subjects, IRBs)
 - Inspections are usually done by appointment, but directed may be unannounced
 - Inspection assignments are issued by FDA Centers.
 - Inspections are conducted during the study or after study completion (could be archived)
- Inspections may be performed during the IND at any phase of product development

What is the focus of the FDA inspection?

- Data auditing is a major component of GCP BIMO inspections conducted at clinical investigator sites.
- FDA inspectors verify:
 - Who did what?
 - The degree of delegation of authority.
 - Where the study procedures were conducted
 - How and where data was documented

Clinical Investigator Regulatory Commitments

- Signing a 1572 is the clinical investigator's commitment in writing to be responsible for the study and agreement to follow:
 - 21 CFR 50 - Protection of Human Subjects
 - 21 CFR 56 - Institutional Review Boards
 - 21 CFR 312 – IND Application
 - 21 CFR 312.64 - Investigator reports – AEs etc
 - 21 CFR 312.62 - Investigator record keeping
 - 21 CFR 312.68 - Inspection of Investigators

Clinical Investigator Regulatory Commitments

- By signing the Form FDA 1572, the Investigator acknowledges legal responsibility and obligation to comply with the law
- The FDA inspector wants to verify that the clinical investigator is in compliance with the FDA Form 1572 and regulations.

What FDA Inspectors Examine

- **FDA inspectors may have access to, copy, and verify any records and reports relating to a clinical study.**
 - **Exception:** QA records are not provided unless FDA is performing “directed” or “for-cause” inspections of a sponsor or monitor of a clinical investigation
 - **Exception:** QA records are not provided unless FDA is performing an inspection with an inspection warrant where access to records is authorized by statute; or in litigation, or part of a judicial search warrant.

Ref: 21 CFR 312.58

How do you prepare for the Inspection?

- When you get the call from FDA to schedule an inspection, be prompt in calling back and providing an acceptable time frame (no delays)
- Clean and organize your site- Ensure the site regulatory binder documentation is organized and complete
 - If files are archived, retrieve and QC files
 - Ensure investigational product storage area is secure and clean
- Review the protocol and what happened during the study
 - Focus on the completeness and follow-up of items noted in monitoring visit reports, SAEs, AEs, and primary/secondary endpoints
- Develop an SOP for FDA Inspections
 - Train staff on procedure/process

Inspection Preparation

- Secure a private room with access to food, drink and facilities prior to the inspection.
- Notify the Sponsor, CRO, and IRB
- Assign a contact person to communicate with the FDA Investigator and to:
 - Track requests and communications
 - Make copies of all requested documents
 - Record Inspector questions
 - Record all answers provide

How long will the Inspection Last?

- The duration of inspection is related to the depth of the inspection and complexity of the study
- Expect anywhere from 1 day to 3 weeks depending on the number of issues identified and the associated risks
- Be prepared and have answers and documents readily available when requested

FDA Inspection Process

- Form FDA-482 gives the FDA authority to enter and inspect the premises at reasonable times
- Upon arrival at site:
 - FDA inspectors issue form FDA-482, Notice of Inspection, to the site
 - FDA present credentials (photo ID badge)

During the FDA Inspection

- Expect probing questions to test clinical investigator knowledge of protocol, regulations, and GCPs
 - Keep answers brief and honest
 - Stay focused on questions
 - Don't be argumentative, keep even tone
 - Be professional and courteous

Sample FDA Questions for Site Staff

- Where was the study conducted?
- Who was involved in the conduct of the study?
- Which tasks were delegated to whom?
- What was the Sponsors monitoring procedure?
- What was the drug accountability procedure?
- How and where was the data recorded?
- What were your IRB reporting requirements?
- How many studies were conducted concurrently?
- How were the rights, welfare and safety of subjects protected?

Closing Meeting with the FDA Inspectors

- The FDA inspector may provide the site with a Notice of Inspectional Observation Form, FDA-483 (lists the observations noted)
- If there are no observations, the FDA inspectors may summarize and only discuss what was found for inclusion in the *Establishment Inspection Report (EIR)*.

After the Inspection

- Field Inspector completes the EIR which is sent to the manager over the area.
- The EIR summarizes, in detail, each and every deficiency or problem noted at the study site
- FDA expects site to file responses to Form 483s within 15 business days
 - If you do not respond within 15 days, a warning letter may be issued

Responding to FDA Form 483s

- Responses to FDA observations should include a Corrective Action and Preventive Action (CAPA) which are fundamental components of an overall Corrective Action Plan (essential to responses)
 - **Corrective action** – State in response what corrections have been implemented (usually more immediate correction)
 - **Preventive action**- Written response should provide detail on how the site will prevent the recurrence of this, or similar violations in the future (may be long-term preventative)

CAPA in Responses to FDA

- Corrective Action -Action taken to eliminate the cause of an **existing** problem, non-conformity, or undesirable situation in order to prevent reoccurrence (reactive)
- Preventive Action -Action taken to eliminate the cause of a **potential** problem, non-conformity, defect or other undesirable situation in order to prevent occurrence (proactive)
- Responses to FDA should have timelines or provide a schedule for completion or implementation of actions

Typical Clinical Investigator Deficiency Categories

- Adhering to the Protocol = Failure to follow the protocol or notify the IRB of deviations
- Maintaining Records – Failure to provide well documented or accurate records
- Consent - ICFs Incomplete, language issues, back dated, process in question
- Drug Accountability
- Adverse Events- AE collection and reporting: from severity determination to reporting errors occur.

FDA Classification of EIRs

- OAI- Official Action Indicated
 - Regulatory and/or Administrative actions will be recommended due to significant objectionable observations
 - Warning Letters and other correspondence

Posted on FDA website

<http://www.fda.gov/oc/gcp> (Enforcement Information)

FDA Compliance Classifications

- NAI- No Action Indicated (most often)
 - No objectionable conditions or practices were found during the inspection (or the objectionable conditions found do not justify further regulatory action)
- VAI-Voluntary Action Indicated
 - Objectionable conditions or practices were found, but FDA is not prepared to take or recommend any administrative or regulatory action.

Regulatory Consequences to Compliance Issues Noted during Inspections

Rejection of study

- FDA issues “refuse-to-file” letter
- Waste of time and money
- Subjects exposed to unnecessary risk
- Ability to conduct research in the future – restrictions placed on clinical investigator
- Disqualification of study data and/or clinical investigator
- Prosecution of Clinical investigator

Administrative Actions

The following administrative actions are available to the FDA:

- Untitled Letters
- Warning Letters
- Reinspection to verify corrective actions
- Regulatory meetings
- For a study subject to 21 CFR 312, placing a clinical hold on the study
- Rejection of data from that site
- Initiation of Disqualification Proceedings
- Consent agreements

References

- FDA LAWs - Federal Food Drug and Cosmetic Act (FFDCA)
- Clinical Investigator Compliance Program Guidance Manual-CPGM 7348.811
- FDA Inspections for Clinical Investigators; Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors
- FDA Warning letters
www.fda.gov/foi/warning.htm
- FDA Disqualified/ Restricted
www.fda.gov/ora/compliance_ref/bimo/dis_res_assur.htm

- Thank you for listening
- Questions?