Audit and Regulatory Inspection

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Overview

Audit

- ICH-GCP, purpose
- When is the audit conducted, audit procedures

Regulatory inspection

- ICH-GCP, purpose
- When is clinical investigator inspection conducted, how is the inspection conducted

- **Findings from the audit**

Audit

ICH-GCP

- A systemic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Audit

Purpose

- The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

Audit

When is the audit conducted?

- **Based on a risk assessment**
  - Critical, pivotal, complex
  - Highly visible
  - Problematic
  - New technology involved
  - Collaborative group involved
  - Previous reference made to Regulatory Authorities
- **On request from a project team or function**
- **For cause**
- **Periodic compliance check**

Audit

Auditing procedures

- Conducting according to sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports
- Guiding by the importance of the trial to submissions to regulatory authorities, no. of subjects in the trial, type and complexity of the trial, the level of risks to the trial subjects, and identified problems
- Documenting audit findings
- Regulatory authorities should not routinely request the audit reports. Regulatory authorities may seek access to an audit report on case by case basis when evidence of serious GCP non-compliance exists, or in course of legal proceedings.
- Providing audit certificate when required by law or regulation

Regulatory inspection

ICH-GCP

- The act by a regulatory authorities of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authorities to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authorities.

Regulatory inspection

FDA conducts clinical investigator inspections to determine if the clinical investigators are operating in compliance with current FDA regulations and statutory requirements.

Regulatory inspection

When are clinical investigator inspections conducted?

- Routinely to verify data that has been submitted to the Agency
- As a result of a complaint to the Agency about the conduct of the study at the site
- In response to sponsor concerns or termination of the clinical site
- At the request of an FDA review division
- Related to certain classes of investigational products that FDA has identified as products of special interest in its current work plan (i.e., targeted inspections based on current public health issues)

Regulatory inspection

FDA personnel audit the study data by comparing the data filed with the Agency or the sponsor, if available, with records related to the clinical investigation.

Regulatory inspection

How are clinical investigator inspections conducted?

- Who performed various aspects of the protocol (e.g., who verified incl/excl criteria, who obtained informed consent, who collected AE data)
- The degree of delegation of authority (e.g., how the clinical investigator supervised the conduct of investigation)
- Where specific aspects of the investigation were performed
- How and where data were recorded
- Accountability for the investigational product
- Monitor's communications with the clinical investigator
- Monitor's evaluations of the progress of the investigation

Finding from audit

Training

- Inadequate staff training:

- Protocol, Protocol amendment, SAE reporting
- ICH-GCP
- US FDA Code of Federal Regulations (CFR) title 21 Food and Drug, FDA1572 and financial disclosure

Finding from the audit

- **Delegation and oversight**
  - Delegation of responsibilities not adequately documented (Authorization form inconsistent / inaccurate / unsigned)
  - Inadequate resources (e.g., staff and facility)
  - Inadequate training and supervision of site staff meant protocol and ICH GCP requirements were not always followed
  - PI did not appear to maintain adequate personal involvement and oversight of study (e.g., no subject visits, no involvement with monitor or auditors)

Finding from the audit

IRB/IEC

- Incomplete or missing submission (e.g., protocol amendment, safety reporting, progress report)
- IRB/IEC request not implemented (e.g., notification of safety update to patient)
- Approval incomplete (e.g., amended documents)

Finding from the audit

Informed consent

- Subject not given current IRB approved ICF to sign at correct time / safety information not updated in time
- Incorrect dating and/or signing (e.g., staff signed ICF on different date to subject, staff dated ICF for subject)
- Study procedures conducted prior to patient consent
- Inadequate documentation of consent process in medical record
- Inadequate translation documentation

Finding from the audit

Protocol adherence

- Schedule of assessments / protocol procedures not adhered to (e.g., procedure for treatment failure, safety reporting, dosing, pregnancy testing, lab testing and provision of patient alert cards)
- Joint assessors not always consistent
- Process for re-entry of screen failures not documented clearly in protocol

Finding from the audit

Study drug

- Dispensing / dosing errors
- Access restrictions to drug storage
- Inadequate temperature monitoring
- Incorrect and/or incomplete drug documentation (e.g., drug records, source document, drug destruction)
- Drug destruction procedure past revision date

Finding from the audit

AE/SAE

- SAE underreporting / late reporting
- Pregnancy underreporting
- SAE documentation was inadequate / inaccurate

Finding from the audit

Lab certification

- Incomplete, expired or unavailable lab certification / accreditation / reference ranges
- Unclear documentation as to which laboratories were used in study
- No written lab procedures or lab validated methods available

Finding from the audit

Site procedure

- Lab reports not reviewed and signed in a timely manner
- Site lacks sufficient systems for preparing and approving written procedures
- Sample storage and shipment procedures were not unclear
- Inadequate flood and fire protection in the archiving

Finding from the audit

Source data / CRF completion

- Incomplete and/or inconsistent source data per protocol and/ or ICH-GCP
- Discrepancies between CRF and source data
- Two sets of source data at site (site unsure which is ‘most correct’)

Finding from the audit

Source data / CRF completion

- Changes to source data not signed and dated
- Records not available to auditor
- CRF pages incomplete or completed late
- Differences in handwriting and un-explained changes in patient diaries

Keep in mind……

If there is no documentation,
it is interpreted as the action is not taken.

Thank you for your attention