Quality and Documentation Tips for Compliance

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Key learning objectives
• By the end of this module you should be able to:
  1. Recognize the importance of quality in clinical trials
  2. Identify key areas for improved documentation and communication leading to better quality
  3. Manage documentation of recruitment efforts effectively
  4. Manage potential document management inconsistencies proactively
Why quality matters

“Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that:

- the rights, safety, and well-being of trial subjects are protected and that the clinical trial data are credible.”

- Introduction to ICH–GCP

TIME

- “The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.”

- ICH–GCP [4.2.2]

- appropriate planning will help you to optimize the time you spend on trial activities
- think about who will be spending time on the trial and how much time they will be spending on it
Time commitment varies at different points in the trial:

- intensive, prolonged effort in the planning stages, culminating in IRB/IEC submission
- subject enrollment may occur all at once or on a regular, extended basis
- subject visits occur on a regular basis
- Adverse Events (AEs) are unpredictable
- a significant increase in commitment is demanded at the end of the trial
- monitoring, audit, and inspection preparation and visits all take time; plan accordingly and be prepared

Documentation

- Each subject visit generates data:
  - records of original data and measurements (source documents)
  - notes to file
  - AE forms
  - Data need to be documented

- Documents need to be:
  - filed securely
  - archived
  - Filing and archiving generate a document trail, which allows all aspects of a study to be reconstructed and is a requirement of ICH–GCP, audits, and inspections

A number of attributes are considered of universal importance to source data and the records that hold that data. These include that the data and records are:

- Accurate
- Legible
- Contemporaneous
- Original
- Attributable
- Complete
- Consistent
- Enduring
- Available when required
Documenting a clinical trial

Before
ICH–GCP lists a minimum of 20 pre-trial essential documents
IRB/IEC approval

During
ICH–GCP lists a minimum of 25 trial essential documents
Study closure

After
ICH–GCP lists a minimum of eight post-trial essential documents

Top 10 2011 FDA Warning Letter Findings for Clinical Investigators

NUMBER TEN
- Failure to obtain IRB approval before making changes in the research
- Failure to obtain IRB approval of a change in the consenting process

NUMBER NINE
- Failure to promptly report to the IRB all unanticipated problems involving risk to human subjects or others
  - a) Failure to promptly report a hospitalization to the IRB
  - b) Failure to promptly report a death to the IRB


NUMBER EIGHT
- Failure to retain records required to be maintained under 21 CFR part 312 until 2 years after the investigation was discontinued and FDA was notified
  - a) Failure to maintain eCRFs for two years after the investigation was discontinued and the FDA was notified
  - b) Failure to retain copies of the screening and enrollment logs for two years after the investigation was discontinued and the FDA was notified
NUMBER SEVEN
- Failure to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects
  - a) Failure to remove the drug label from the package dispensed to the subject and affix it to the drug accountability records
  - b) Failure to maintain an accurate record of drug received at your site
  - c) Failure to adequately document transfer of study drug from one approved facility to another
  - d) Failure to record dates and quantity of all investigational product dispensed

NUMBER SIX
- Failure to obtain informed consent in accordance with the provisions of 21 CFR part 50
  - a) Failure to use an informed consent document that had been approved by the IRB
  - b) Failure to ensure study subject signed the informed consent document prior to involvement in the study

NUMBER FIVE
- Failure to report promptly to the IRB all changes in the research activity
  - a) Failure to inform the IRB that enrollment was closed
  - b) Failure to inform the IRB that recruitment for a study was temporarily placed on hold by the Sponsor secondary to deficiencies at your study site
  - c) Failure to inform the IRB that your site was closed by the Sponsor secondary to significant noncompliance with GCP
NUMBER FOUR
• Failure to protect the rights, safety, and welfare of subjects
  • a) Failure to ensure a pharmacist or qualified person prepared the investigational product

NUMBER THREE
• Failure to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation
  • a) Failure to sign the source physical exam record
  • b) Failure to provide evidence of the occurrence of an adverse event in the source documents
  • c) Failure to accurately complete case report forms based on the information documented in the subject’s source documents
  • d) Failure to record dosing decisions or provide dosing orders
  • e) Failure to record vital sign assessments in the subject’s source documents

NUMBER TWO
• Failure to personally conduct or supervise the clinical investigation
  • a) Failure to adequately supervise a study coordinator
  • b) Failure to adequately supervise a research nurse
  • c) Failure to review study documentation including letter and email correspondence from monitors, sponsors and IRB
  • d) Failure to assess adverse events
NUMBER ONE

- Failure to ensure that the investigation was conducted according to the investigational plan
  - a) Failure to obtain protocol assessments such as physical exams, labs, ECGs, scans, etc.
  - b) Failure to report adverse events and SAEs as required by the protocol
  - c) Failure to review lab or other test results in a timely manner
  - d) Failure to adequately screen subjects to ensure they meet enrollment criteria
  - e) Failure to assess adverse events per the requirements in the protocol
  - f) Dispensing investigational product to a subject who is not eligible for the trial
  - g) Dispensing doses of investigational product not indicated by the protocol

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European Medicines Agency (EMA)
Top Ten Findings

- 1. Essential Documents (investigational site)
- 2. Supply, storage, retrieval and destruction of test article
- 3. Monitoring
- 4. Clinical Study Report
- 5. Assay Validation
- 6. Source Documentation (investigational site)
- 7. Informed Consent process
- 8. Protocol Compliance (safety reporting)
- 9. Qualification/Training (investigational site)
- 10. Delegation of Duties (investigational site)

Source: Annual Report of the GCP Inspectional Unit—Year 2008. 29 March 2009

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Standard Operating Procedures (SOPs)

- "Detailed, written instructions to achieve uniformity of the performance of a specific function." 
  - ICH-GCP [1.55]

- SOPs are designed to:
  - ensure consistency
  - assign responsibility
  - promote compliance

- "It is good clinical practice to have SOPs in place and to ensure they are clearly documented.

Note: If SOPs are present you are obligated to follow them, be aware they are subject to change."
Regs vs. SOPS

- What does the regulation state?
- What does the sponsor's SOPs state?
- What does my institution/site state?
- Site specific SOPs need to be considered in addition to the sponsor's protocol/requests
- How do we resolve conflicts?

Logs – Sponsor Provided?

- Signature and Delegation Log
- Subject Screening Log
Investigator Oversight

- Is there an open environment?
- What steps can you take?
- How do you document?

Additional Documentation

- Management (team meetings with minutes/templates/etc)
- Consent Forms (color-coding/version dates)
- Notes to File
- Deviations/Violations – IRB notification
Recruitment potential

"The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period."

ICH–GCP [4.2.1]

Recruitment Plans

- Is one provided by your sponsor?
- What should be included?
- How frequently should it be updated?
What are some other potential problem areas for documentation at your site?

Wrap-up
1. Recognize the importance of quality in clinical trials
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