Quality Control
and
Quality Assurance
in Clinical Trial

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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)

Quality is teamwork

There are many people/groups involved in the regulation and quality of clinical trials

- **Investigator and study team**
  - protocol compliance
  - standard processes
  - regulations
- **Sponsor**
  - quality control & quality assurance: on-site monitoring & audit
  - SOPs
- **Regulatory authorities**
  - inspections
- **Data protection agencies**
  - inspections
- **IRB/IEC**
  - continuing review

Sponsor's role in Quality Assurance

- Sponsor is responsible for
  - Implementing & maintaining quality assurance (QA) and quality control (QC) with written SOP's (ICH-GCP 5.1.1)
  - Securing agreement from investigator/institution and/or with any other parties on direct access to all trial-related sites, source data/documents, and reports **for monitoring, auditing, and inspection** (ICH-GCP 5.1.2)
  - Applying QC to each stage of data handling (ICH-GCP 5.1.3)

Should be in writing (ICH-GCP 5.1.4)

- Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial.
- Confidentiality of subjects' identities and sponsor's proprietary information should be maintain

(ICH-GCP 1.21)

Quality Control VS Quality Assurance

	QC	QA
Role	▪ Part of the study conduct to ensure quality	▪ Third-party assurance of quality
Responsible persons	▪ Study team ▪ Monitor	▪ Independent unit of sponsor organization ▪ Auditor
Activities **Timing**	▪ Monitoring ▪ Study duration	▪ Audit : systemic & independent examination ▪ One time point: routine & for cause
Summary	▪ Procedures that ensure that the process is in control and ▪ "makes things correctly"	▪ Procedures that verify that QC procedures are effective and ▪ "the correct things are made"

Monitoring

Who is the monitor?

- A team member
- A data-checker
- Someone who checks the site team's work

Introduction to monitor
- a professional
- a valuable resource and partner to the study team
- the main line of communication between the sponsor and the investigator
- a key contact for trial-related issues

Monitor (1)

- Trial monitoring
  - Purposes: (ICH-GCP 5.18.1)
    1. Right and well-being of human subjects are protected
    2. Trial data are accurate, complete, and verifiable from source documents
    3. Conduct of trial complies with current approved protocol, GCP, applicable regulatory requirements
  - Monitors: (ICH-GCP 5.18.2)
    - Appointed by sponsor
    - Qualified
    - Thoroughly familiar with study drug, protocol, ICF, SOPs, GCP, applicable regulatory requirements

Monitor (2)

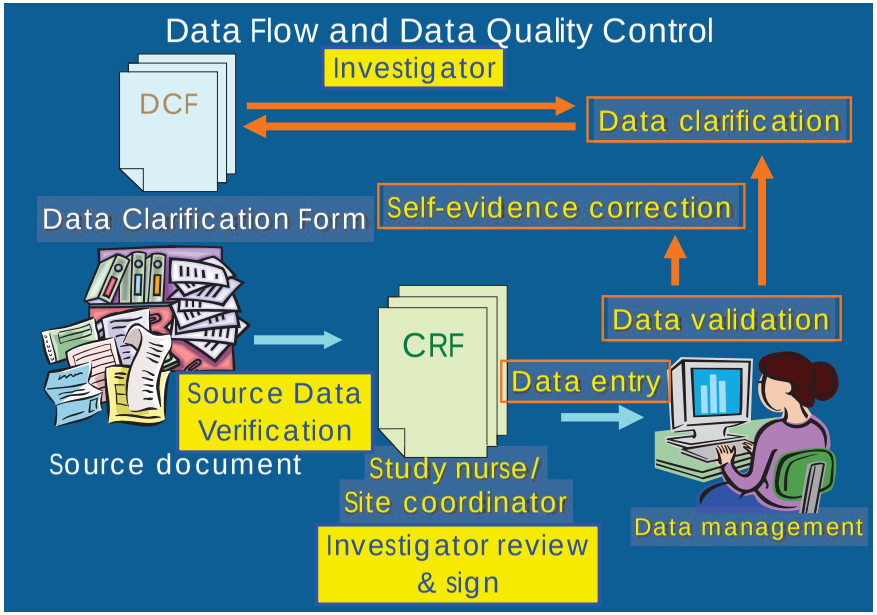
- Monitor's responsibilities (ICH-GCP 5.18.4)
  - Main line of communication between sponsor and investigator
  - Verify
    - investigator & site staff qualification
    - adequacy of resources/facilities
    - appropriate storage of drug
    - use of study drug
      - perform drug accountability document review and reconciliation

Monitor (3)

- Monitor's responsibilities (ICH-GCP 5.18.4)
  - Verify
    - compliance to protocol, GCP, SOP, and applicable regulatory requirements,
      - communicate or take appropriate action to correct and/or prevent the deviations
    - time of ICF obtained
    - eligibility of participating subjects
  - Track subject recruitment and retention

Monitor (4)

- Monitor's responsibilities (ICH-GCP 5.18.4)
  - Ensure
    - safety report complied with protocol, IEC, GCP, SOP, and applicable regulatory requirements
    - accuracy and completeness of the CRF entries, source data/documents, and other trial-related records
    - appropriate correction, addition, or deletion of CRF entry
    - all essential documents are complete, kept up-to-date, and maintained



Monitor (4)

- Monitor's responsibilities (ICH-GCP 5.18.4)
  - Ensure
    - communication between investigator and IRB/ IEC complied with GCP, SOP and applicable regulatory requirements
      - protocol (protocol amendment) approval
      - safety reporting
      - protocol violation (if required)
      - study progress report
      - study completion/termination
      - final study report

Monitoring Visit

- Types of site monitoring
  1. Pre-trial site assessment (Pre-study visit)
  2. Study initiation visit
  3. Monitoring visit (Periodic visit)
  4. Study close-out visit
- Monitoring Procedures (ICH GCP 5.18.5)
  - follow the sponsor's SOPs and those procedures specified for monitoring a specific trial (Monitoring Guidelines).

Extent and Nature of Monitoring (1)

- The sponsor should
  - ensure that the trials are adequately monitored
  - determine the appropriate extent and nature of monitoring,
    - based on the objective, purpose, design, complexity, blinding, size, and endpoints of the trial.

(ICH GCP 5.18.3)

Extent and Nature of Monitoring (2)

- In general there is a need for on-site monitoring, before, during, and after the trial
- In exceptional circumstances, the central monitoring may be determined
  - in conjunction with procedures such as investigators' training and meetings, and extensive written guidance.
  - may use statistically controlled for selecting the data to be verified

(ICH GCP 5.18.3)

Frequency of monitoring visit

- The number and timing of monitoring visits is dependent on:

Study issues	Site issues
• Study objectives • Study design • Phase of clinical trial: early phase • Complexity • Blinding • Size: # of subjects, sites • Study endpoints: mortality • Data collection	• Experience of the investigator and study team • Logistics • Problems encountered: protocol & GCP compliance • Number of subjects enrolled

- The frequency of visits will also vary before, during, and after the study

Monitoring visit

- Before a monitoring visit, make sure that

PI/staff are available to answer questions

Documents are available for review and SDV

Space is available for the duration of the visit

Time is scheduled for the visit

Monitoring Report (1)

- Monitoring report
  - Determine responsibilities of sponsor on the trial
    - Monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.
    - Sponsor/designee should review and follow up of the monitoring report
      - The review and follow-up should be documented.

Monitoring Report (2)

- Monitoring Report
  - Monitoring Report should include (ICH GCP 5.18.6)
    - monitoring date
    - name of the monitor
    - name of the site, investigator or other individuals contacted
    - a summary of what is reviewed,
    - significant findings/facts, deviations and deficiencies, resolutions,
      - Corrective actions and preventive actions taken to secure compliance

Study Close-out Monitoring

- After the trial:
  - making sure that all study data *(including safety data)* have been collected
  - informing the site of its archiving responsibilities
  - checking the return/destruction of the investigational product
  - making sure that the IRB/IEC is notified of study closure

Audit & Inspection

Differences between audit and inspection

	Audits	**Inspections**
Who conducts them?	Independent unit of the sponsor company	Regulatory authorities, IRB/IEC, Data Protection Agencies
What do they check?	Trial conduct and compliance with: • protocol • ICH–GCP • regulatory requirements	
When do they occur?	Any time before, during, or after the trial	
Why do they take place?	• randomly • for cause	
How can you help?	• follow the protocol • document and file everything	

Audit: Purpose & Type

- Audit
  - Purpose: (ICH-GCP 5.19.1)
    - To evaluate trial conduct and compliance with the protocol, SOPs, GCP, and applicable regulatory requirements
    - Independent of and separating from QC
  - Type of audit
    - Routine/surveillance audit
    - For-cause audit

Audit is a learning process & a part of continuous process improvement

Audit: SOP & Audit Plan

- Audit (cont.)
  - Procedures: (ICH-GCP 5.19.3)
    - SOP: indicate what to audit, how to audit, the frequency of audits, and the forms and content of audit reports
    - Audit plan: guided by
      - importance of trial to submission to regulatory authorities,
      - no. of enrolled subject,
      - type & complexity of trial,
      - level of risk to the trial subjects,
      - any identified problem(s)

Audit Process

- Audit
  - Process:
    - Scheduling of audit/inspection
    - Pre-audit review of sponsor file (by sponsor auditors)
    - Opening meeting
    - Review of study conduct
    - Discussions with the investigator and site staff
    - Closing meeting
    - Issuing the report : findings/observations (critical, major, minor)

Audit Process

- Audit
  - Process:
    - Follow-up of development and implementation of the corrective and preventive action plan (CAPA) until all findings/observations resolved
    - Closing the audit

Audit Process

- Audit
  - Procedures: (ICH-GCP 5.19.3)
    - Regulatory authorities (RA) should not routinely request the audit reports
      - RA may seek access to an audit report when serious of GCP noncompliance exists or in the course of legal proceedings

What auditor review

- Study Conduct:
  - Who did what; the degree of delegation of authority
  - How and where data were recorded
  - How test article (e.g. drug) accountability was maintained
  - Where & how specific aspect/procedure of the study were performed
  - How the monitor communicated with the clinical investigator
  - How the monitor evaluated the study's progress

What auditor review

- Data Review
  - Diagnosis
  - Subject eligibility
  - Informed consent
  - Trial procedures & scheduling
  - Outcome assessment
  - Concomitant medications
  - Safety monitoring

Possible Audit Findings or Observations

- Trial issues:
  - Compliance with applicable regulation & SOP
  - Drug: label, storage, accountability, destruction
  - Trial documentation and archiving
  - Trial monitoring
  - Data validity (data quality & integrity):
    - absence of supporting source document
    - inaccurate/incomplete source document
    - inconsistency between CRF & source document
  - IRB/IEC approval and communication etc.

Possible Audit Findings or Observations

- Subject issues:
  - Informed consent form and informed consent process
  - Study entry and documentation
  - Eligibility: diagnosis, inclusion & exclusion criteria
  - Safety reporting & follow up
- Site issues:
  - Site staff qualification & delegation, training,
  - Facilities: equipment validation, lab accreditation etc.

Possible outcomes of audits/inspections

Minor observation	• Deviations/deficiencies will not adversely affect subjects/data, but should be dealt with appropriately
Major observation	• The quality/integrity of data or rights and safety of subjects may be adversely affected if practices continue
Critical observation	• The quality/integrity of data or rights and safety of subjects are adversely affected

The type of observation will determine the action taken by the sponsor or regulatory authority

Possible outcomes of audits/inspections

- USFDA Inspection Classification
  - NAI: No action indicated
    - No objectionable conditions or findings
  - VAI: Voluntary action indicated
    - Objectionable condition or findings
    - But not at threshold to take or recommend administrative or regulatory actions
  - OAI: Official action indicated
    - Serious objectionable conditions
    - Regulatory action recommended: warning, disqualified

Common observations in audits & inspections

- Non-compliance with protocol
- Informed consent problems
- Inadequate/missing source documents/CRF
- Inadequate record keeping
- Inadequate IRB/IEC communication & documentation
- Qualification & inappropriate delegation; inadequate PI oversight
- Inappropriate drug storage & accountability; Inadequate safety reporting
- Fraud/misconduct

Falsification of data

- **Consequences of falsification:**
  - places study subjects at risk
  - jeopardizes the reliability of submitted and/or published data
  - investigators will not be selected by sponsors
  - legal action:
    - fine
    - imprisonment
    - loss of medical license

Preparation for an Audit/Inspection

- Know your study: status, protocol, related process/ system and SOP
- Know your study staff
  - Know your staff role & responsibilities
  - Ensure your staff know their responsibilities and understand their responsible process/system
  - Ensure your staff are qualified
- Know your study documents
  - If it's not clear ask what documents are required
  - However all documents should be available
  - Documents are organized, complete, current

Preparation for an Audit/Inspection

- Know your study documents
  - Ensure study documents are able to verify
    - Study drug/device accountability
    - Staff qualification, training, and appropriate assignment
    - Regulatory compliance
    - Protocol compliance and appropriate handling of deviations
    - Data quality and integrity
    - Identification and reporting of adverse event and follow-up adequacy
    - Subject existence
    - Subject eligibility
    - Informed consent

Preparation for an Audit/Inspection

- Reserve a separate room for auditor/inspector
- Ensure sponsor, investigator and site staff are available
- Assign a person to will be accompany auditor/ inspector at all times
- Ensure accessibility to photocopy machine

Responding to an audit (1)

- Don't be panic
- Contact sponsor immediately
- Retrieve all study records
- Cooperate with the auditing,
- Provide only what is requested
- Respond promptly to any auditing reports or letter from sponsor and regulatory author

Responding to an audit (2)

- **Do**
  - Professional
  - Controlled
  - Courteous
  - Helpful and responsive
- **Don't**
  - Defensive
  - Resentment of opposition
  - Clash of personalities
  - Impressed

Responding to an audit (3)

- **Communication: when talking avoid**
  - Personal opinion
  - Personal feeling
  - Descriptive expression
  - Jokes
  - Slang
  - Company specific abbreviation

Responding to an audit (4)

- **Communication: when talking do**
  - Answer the question nothing more
  - Start with keeping it simple
  - Go into more detail if needed
  - Keep it structured
  - Speak slowly
  - Test for understanding

Responding to an audit (5)

- **Communication: listening**
  - Actively
  - Intelligently
  - Carefully
- **Limit yourself to the scope, the question**
  - Fact
- **If you don't know,**
  - tell them you don't know
  - Look in the documentation
  - And give the correct answer

Responding to audit and inspection findings

- **Audit**
  - site informed of findings at closing meeting
  - initial report sent to sponsor
  - sponsor meets with site to discuss remedial actions
  - remedial actions agreed, implemented, and documented (corrective action & preventive action plan and implementation)

Responding to audit and inspection findings

- **Inspection**
  - written report sent by regulatory authority to investigator/ sponsor
  - investigator sends written response to regulatory authority describing planned or already implemented actions
  - follow-up letter from the competent authority
  - follow-up inspection

Written Response

- Evaluation of the extend of the problem/finding
- Assessment of the root cause of the problem/ finding
- Corrective actions
  - Not just a plan to correct a problem; but
  - What was corrected and when was it completed
  - Is the problem/finding systemic
- Preventive actions to prevent recurrence of the problem/deficiency
  - Implementation and time frame
- Supportive documents

You're ready

- If processes are being followed correctly at the site then
  - the investigator and study team should not be concerned about the occurrence of monitoring, an audit, or an inspection
- "Understand, inspections are important but nevertheless routine and nothing to be alarmed about."

US FDA

You're ready

Audit or inspection.....a fact finding,
not a fault finding process !

What is not documented...dose not exist !

Question & Answer

Thank You