

Quality Management in Clinical Research

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Overview

- Quality Management
 - Establishing and ensuring the quality of processes, data, and documentation associated with clinical research activities
- Multi-disciplinary activity
- Occurs throughout the study, not just one point in time
- Trend toward risk-based management

Purposes of Quality Management

- Provide standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials
- Provides quality data
- Ensures the rights and well-being of the patient are protected

Human Subject Protection (HSP) +
Quality Data = GCP

“Quality” Guidances

[International Conference on Harmonization (ICH) GCP Guidelines]

- All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification (2.10)
- Systems with procedures that assure the quality of every aspect of the trial should be implemented(2.13)
- Quality control (QC) should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly (5.1.3)

“Quality” Regulations & Guidance

(U.S. Food and Drug Administration)

- Investigator Responsibilities
 - Ensure adherence to the study protocol, regulatory requirements, and GCP standards in conducting the trial
- Sponsor Responsibilities
 - Select, train, and support investigators and monitors
 - Monitor study progress

Terminology: QA & QC

Quality Assurance (QA)

Planned, systematic and independent evaluation of trial-related activities and documents to verify data were generated, collected, handled, analyzed, and reported according to protocol, SOPs, and GCPs

Quality Control (QC)

An aggregate of activities within the quality assurance system signed to verify that clinical data are generated, collected, handled, analyzed, and reported according to protocol, Standard Operating Procedures (SOPs), and GCP

Terminology: Quality Improvement (QI)

- Result of QA and QC
- Identify trends and areas for improvement
- Develop plan to:
 - Identify root cause of problem
 - Intervene to reduce or eliminate problems
 - Take steps to correct process(es)
- Identifying solutions:
 - Assess work flow and time management activities
 - Develop tools for source documentation
 - Assess training needs
 - Involve appropriate staff in resolution

Data & Safety Monitoring Plan (DSMP)

- General plan contained in the research protocol to ensure the safety of the subjects and to ensure the validity of the data
- Tailored to the nature, size, complexity, and risks of the research
- Plan should be described in the protocol application/protocol
 - Need IRB review and approval

Elements of the DSMP...

- Roles and responsibilities for gathering, evaluating and monitoring the data
 - Monitoring mechanism [e.g., Individual Medical Monitor, Data Monitoring Committee (DMC)]
 - Frequency of the monitoring
 - Information to be monitored
 - What safety information will be collected (including serious adverse events)
 - How safety information will be collected (e.g., via case report forms, at study visits, by telephone calls with participants)
 - When data will be collected (e.g., frequency; when collection starts)

...Elements of the DSMP

- Roles of investigators, research staff, sponsor, and monitoring committee/entity
- Plans for any interim analyses and/or futility analyses
 - Stop or change rules

Auditing

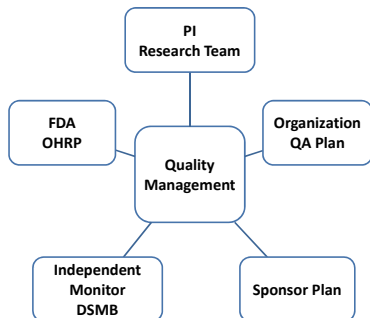


Monitoring



Monitoring + Auditing =
Solid Assurance of Quality

Monitoring Plans



PI/Research Team

- PI will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities
- Team will meet on a regular basis
 - Decisions about enrollment
 - Review adverse event and response data
- All data collected in a timely manner and reviewed by the PI
- Adverse events and protocol deviations will be reported
- Statistical/statistician review

Organization

- Risk based
- Identify aspects of GCP that need to have quality review
- Develop matrices
 - Pre-post SOP development
 - Prior deficiencies
 - Include frequency
- Use for quality improvement

Sponsored Clinical Trials

- Sponsor is responsible for the initiation, management, and/or financing of a clinical trial
 - Sponsor typically does not conduct the investigation
 - Hold an IND (Investigational New Drug) or IDE (Investigational Device Exemption)
- Sponsor can be:
 - Individual
 - Pharmaceutical company
 - Government agency
 - Academic institution
 - Private organization
 - Other organization

Sponsor Quality Management Plan

- Site visits
 - Pre-study qualification visit
 - Initiation visit
 - Monitoring visit
 - Close-out visit
- Audits

Pre-study Qualification Visit

- Determine the site's ability to conduct the clinical trial prior to commencement of the investigation
- Goal of the pre-study qualification visit:
 - Visit the site
 - Meet with study staff
 - Inspect the facilities
- Need to determine who the sponsor wants to meet with and what they want to see at the site
- Allow 2-3 hours for the visit

Initiation Visit

- Performed by the CRA (Clinical Research Associate)
- Includes CRA, PI, and clinical research site staff
- Purpose: review the protocol and required procedures and clarifying any investigator questions prior to activation of clinical trial
- Visit timing is typically after IRB approval and prior to 1st participant enrollment
- NOTE: For multi-site studies, sponsors may conduct an Investigator meeting at one location, instead of numerous individual site initiation visits

Monitoring Visit

- Performed by the CRA
- Visit timing occurs at pre-determined intervals, depending on phase of study, beginning after 1st subject is accrued
- Review of data will be performed for accuracy and completeness
- Review of protocol conduct
- CRA will meet with the site primary contact

Close-Out Visit

- Performed by the CRA
- Visit timing occurs once the investigation has reached its targeted accrual and all subjects have completed the follow-up stage
- Review all regulatory documents and product accountability records
- Review record retention guidelines

Sponsor's Audits

- Sponsor's QA department may chose to audit a site:
 - as preparation to filing marketing application
 - result of monitoring findings
- Ensures source documentation is complete and that the site is well-organized and prepared for the inspection
- Also may be done:
 - for review of monitoring practices (ie, QA of the monitor)
 - aid in identifying and correcting problem areas
 - provide suggestions to improve site performance

Monitoring Plans



Independent Monitor

- May be used for:
 - More than minimal risk
 - Multi-site protocols
 - Investigator who may have a potential conflict of interest
 - FDA-regulated research

DSMB

- An independent and external group
- May be established to assess:
 - the progress of a clinical trial
 - safety data
 - critical efficacy variables
- Make recommendation
 - Continue, modify or terminate a trial

DSMP vs. DSMB

DSMP

- Can include members of the research team
- Must describe standardized review plan
 - What will they review
 - When will they review
- Good idea to have if there are ANY potential risks associated with the proposed study

DSMB

- Independent from the research team
- Must have described standardized review plan
 - What will they review
 - When will they review
- REQUIRED for certain clinical trials based on funder or sponsor

FDA Inspections/Audits

- Bioresearch Monitoring Program (BIMO)
- Goals:
 - Ensure quality and integrity of data and information submitted to the FDA
 - Protect human research subjects
- Information Sheet
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126553.pdf>

OHRP Compliance Oversight Investigation

- OHRP's Division of Compliance Oversight (DCO) reviews institutional compliance with the federal regulations governing the protection of human subjects in HHS-sponsored research 45 CFR 46.
- 2 types of inspections/visits:
 - For cause
 - Not for cause
- <http://www.hhs.gov/ohrp/compliance/evaluation/ohrpcomp.pdf>

Preparing for a Successful “Quality Visit”

- Regulatory review
- Source document review
- CRF review
- If applicable, pharmacy review
- Tips for success

Regulatory Review...

- **All** protocol versions and approvals
- All IRB correspondence (e.g., Continuing reviews, Unanticipated Problem reporting)
- All participant original consents are in the medical record, signed & dated per Institution policy
- **All** Investigator Brochure versions, if applicable

...Regulatory Review

- **All** versions of Form 1572, if applicable
- CVs, licenses and Financial Disclosures for all Investigators – signed and dated, if applicable
- Lab certifications and normal ranges
- All Sponsor correspondence, if applicable
- Delegation of Responsibility/Signature Log as needed

Source Document Review

- Assure medical records contains:
 - All laboratory reports
 - X-ray, scan reports
 - Practitioner notes
 - Procedures documenting study parameters
 - Informed consent **process** documentation
 - Drug compliance/administration notes
- Obtain missing information **or** document why unobtainable
- Laboratory reports and procedure reports are reviewed and signed by PI (if applicable)

CRF Review

- Assure CRF's are complete, accurate, up to date
- Review adverse events
 - Assure attribution of events is documented
- Review concomitant medications
 - Assure stop & start dates are recorded
- Review study medications
 - Assure stop & start dates are recorded

Pharmacy Records Review

- Pharmacy should review drug dispensing records prior to visit
 - Drug Accountability Record Forms (DARFs)
- Assure drug count is accurate
 - Disposal of returned meds
- Assure notes to file are written for any discrepancies

Securing Room/Records and Staff

- Review organization's procedure
- NIH resources
 - <http://intranet.cc.nih.gov/medicalrecords/>
 - Regulatory Audit Guide
 - Regulatory Audit Scheduling Form
- Inform pharmacy of visit and schedule appointment
- Make sure PI and others will be available
- If multiple visits occur simultaneously, make sure each group has a separate room to ensure privacy and confidentiality

Steps to Make the Visit Go Smoothly...

- Arrange all source documents, CRFs and regulatory files in monitor room
 - Access to electronic systems
- Provide only records requested
- Greet reviewer and escort to the designated room
- Review format of medical and research record
- Orient reviewer to appropriate areas such as bathroom, phone

...Steps to Make the Visit Go Smoothly

- Confirm appointment times with PI and Pharmacy
- Check in on reviewer in short intervals to ensure all questions are answered
- Escort to PI or pharmacy at appointed times
- Allow time for corrections
- For activities that occur over multiple days, ensure that medical and research records are kept in a locked room

Common Deficiencies

- Failure to follow the protocol
- Failure to keep adequate and accurate records
- Problems with the informed consent form
- Failure to report adverse events
- Failure to account for the disposition of study drugs

Quality Challenge

Case Report Form(CRF) vs. Protocol

- Ensure that data generated during the study reflect what is specified in the protocol

CRF vs. Source Documents

- Compare data in CRF and data collected in source documents for accuracy

Database vs. CRF

- Ensure data analyzed are data recorded in the CRF

Regulatory Compliance

- Ensure compliance with applicable regulations and guidances

Components of a Quality System

- Personnel roles and responsibilities
- Policies and procedures
- Training
- Quality assurance and auditing
- Document management, record retention and reporting
- Corrective and preventive action

Personnel Roles and Responsibilities

- All research personnel knowledgeable about:
 - Regulations
 - Guidances including ICH GCP
 - Internal policies and SOPs
- Delegation of duties per team member's ability, training, and licensure compared to protocol procedures
- Written plan for key personnel coverage

Policies and Procedures

- Prior to writing protocol, know institutional policies and SOPs including:
 - Protocol review procedure
 - Handling of biologic specimens
 - HSP
 - Confidentiality
 - Data management
 - Procedure for scientific misconduct
- Manual of operations
 - Protocol-specific SOPs

Training

- Good Clinical Practice (GCP)
- Human Subject Protection (HSP)
- As applicable
 - Investigational product
 - Instrument use
 - Survey administration
- Documentation of training
 - SOP training
 - Periodically repeated
- Assess adequacy of training (knowledge testing)

Document Management, Record Retention & Reporting

- Document handling, including:
 - Conventional naming
 - Tracking
 - Filing
 - Version control
 - System back-up
- Standardization of data collection
- Archival procedures
- Securing and restricting “files”

Correction and Preventive Action

- Identify potential or real problems and take action to prevent or correct
 - Evaluate why problem occurred
- Develop a plan:
 - Corrective action plan (CAP)
 - Preventive plan
- Document the whole process

Assessing the Quality Practices

- Are protocols written clearly? Do you know what and when procedures are to be implemented?
- Are staff checking their own work or relying on others?
- Does the organization have a quality management plan for monitoring protocol adherence and data collection?
- Are there clinical research SOPs including humans subject protection and data management?
- How are case report forms developed?
- Do you know what to do if you had a quality inspection of your study site?

<http://www.nidcr.nih.gov/Research/toolkit/>

<https://accrualnet.cancer.gov/>

<http://www.ct-toolkit.ac.uk/>

