Data and Non-Data Quality Control in Clinical Studies

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Overview

• Quality Management
  – Process of establishing and ensuring the quality of processes, data, and documentation associated with clinical research activities
  – Multi-disciplinary
  – Occurs at multiple level:
    • Research team/Individual site
    • Study
    • Sponsor
    • External

Good Clinical “Research” Practice (GCP)

• 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” Regulations
(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

“Quality” Guidelines
[International Conference on Harmonisation (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)
• 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)

Terminology...

Quality Control (QC)
An aggregate of activities designed to verify that clinical data are generated, collected, handled, analyzed, and reported according to protocol, Standard Operating Procedures (SOPs), and GCP

Quality Assurance (QA)
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
**Terminology: Quality Improvement**

- Result of QC and QA
- 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

**...Terminology: Monitoring**

- Act of overseeing the progress of a clinical trial:
  - On-site
  - Central
- Source document verification (SCV) for all research participants
- Ensuring that the study is conducted, recorded and reported in accordance with protocol, SOPs, GCPs, and all applicable regulatory requirements
- Each protocol will outline a data safety and monitoring process and plan
- Some studies may require a data safety monitoring board/committee (DSMB/DSMC)

**...Terminology: Auditing**

- Systematic and independent examination of the trial related activities and documents
- Snapshot in time of a subset of participants
- Determine whether the trial related activities were conducted and data recorded accurately, analyzed and appropriately reported according to the protocol, SOPs, GCP, and all applicable regulatory requirements
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 polices 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 contact
  - 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?
Levels of Quality Management Plans

- PI/research team
  - Should be included in the protocol
- Organization
- Data and safety monitoring board/committee (DSMB/DSMC)
- Sponsor (IND/IDE) plan
- Regulatory authority
- Multiple plans per study

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

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
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

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...**

- Purpose is to ensure the PI and site staff understand:
  - Roles/responsibilities/regulatory obligations
  - Protocol procedures
  - CRF completion instruction review
  - Requirements for records management/retention
  - Drug handling requirements
  - Enrollment and consent procedures
  - Expedited adverse event reporting procedure
  - Patient recruitment resources
- Identify potential problems and concerns

**...Initiation Visit**

- Timing of visit:
  - Prior to patient enrollment
  - After all essential documents in place
  - After supplies received
  - After IRB approval
- Attendees
  - Sponsor/CRO
  - Site
- Preparation
- Post-visit
Monitoring Visit...

- **Purpose**
  - Review progress of a clinical study
  - Ensure protocol adherence
  - Assure accuracy of data
  - Assure safety of subjects
  - Regulatory Compliance (CFR & GCP)

...Monitoring Visit

- **Timing/Frequency**
  - Depends on:
    - Complexity of the protocol
    - Disease being studied
    - Rate of recruitment
    - PI/staff experience
    - Site performance
    - Sponsor’s SOPs

- **Attendees**
  - Sponsor/CRO
  - Site
  - Preparation
  - Post-visit

Close-Out Visit

- **Purpose** is to review:
  - All regulatory documents
  - All drug accountability record forms (DARFs)
  - Review record retention guidelines

- **Timing:**
  - Study is complete and Investigator obligations fulfilled
  - All data has been retrieved, entered and database locked

- **Attendees**
Sponsor’s Audits

• Sponsor’s QA department may choose to audit a site:
  – as preparation to filing the NDA/BLA
  – 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

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

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 Monitoring Visit

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

Regulatory Review...

- All protocol versions and approvals
- All IRB correspondence
  - Amendments
  - SAEs
  - Continuing Reviews
- All participant original consents are in the medical record, signed & dated per Institution policy
- All Investigator Brochure versions

...Regulatory Review

- All versions of Form 1572
- CVs, licenses and Financial Disclosures for all Investigators – signed and dated
- Lab certifications and normal ranges
- All Sponsor correspondence
- 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...

• NIH Specific: Ensure monitor’s current CV is in Medical Records
• 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

...Steps to Make the Visit Go Smoothly...

• Review format of medical and research record
• Orient reviewer to appropriate areas such as bathroom, phone
• Confirm appointment times with PI and Pharmacy
• Check in on reviewer in short intervals to ensure all questions are answered
...Steps to Make the Visit Go Smoothly

- 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

Guiding Principles

- Source documents need to be accurate and complete
- Data abstraction should occur in real time
- QC/QI is the responsibility of every research team member
- QC/QI should be completed on all protocol data for all protocols
- QC/QI should be proactive and ongoing
- Each team member should know and understand the roles and responsibility of each team member

Resources
Improving the Clinical Research Process

- Human factors
- Systems and standardization
- Integrated plans
- Training
- Unblinding
- Disaster planning
- Beta-testing
- Communication
- Data management
- Audits


Questions

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