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

“Quality” Guidances
[International Conference on Hamonization (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 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

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 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?

Resources

Selected References

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Questions

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