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U.S. FOOD & DRUG ADMINISTRATION

Quality Management Systems and Quality By Design

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Learning Objectives

- To understand
  - Basic characteristics of clinical trials of quality
  - The roles that quality management systems, quality by design principles, and risk-based monitoring play in ensuring data reliability and trial participant protection in the clinical development of new medicinal products

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Importance of Quality in Clinical Research

- Clinical research is the means by which preventive, diagnostic, and therapeutic interventions are evaluated
- Relied on for decision making by
  - Patients and Caretakers
  - Physicians/Medical Personnel
  - Industry
  - Regulators

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A Reminder: Clinical Trials of Quality

- Scientific question is important; there is a need to produce high-quality evidence to inform decision making on use of a preventive, diagnostic, or therapeutic intervention
- Trial design is adequate to answer this scientific question; if study well conducted the results will be credible
- Data produced are sufficiently accurate and reliable (fit for purpose) so that they may be used for decision making
- The rights, safety, and welfare of trial participants have been adequately protected

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System Inertia

- Despite increasing costs of clinical development programs, in particular costs attributed to clinical trials, problems with trial conduct persist impairing our ability to attain high-quality evidence
- Patterns of critical audit findings have shown little change over years
- CDER's BIMO Inspection Program shows little change in patterns of regulatory violations over the years*

* http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM438250.pdf

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Need for Change:
Moving from Tra…hes …..

- Siloes … source manag… owledge sharing
- Tradition… ocused primarily … iption checking)
- Assessmen… g after study completion (routine spo… egulatory inspections)

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Need for Change:

….. to Proactive Quality and Risk Based Approaches

Quality Management Systems

Quality by Design

Risk Based Monitoring

Data Management Plan,
Safety Monitoring Plan,
Plans, Plans, Plans, Etc.

Quality Management System

- A Quality Management System (QMS) is an integrated system through which organizations can systematically plan and achieve quality objectives linked to their broader strategic goals

- Fully implemented across many industries, though use in clinical development arena lagging

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Quality Management System

- Well described – International Standards Organization (ISO 9000, 9001, 9004)

- A reasonable assumption that principles and experience from other sectors may be leveraged to inform development of quality management systems in the clinical development arena

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Quality by Design (QbD)

- Premise: Quality in clinical trials is defined as the absence of errors that matter.

  What do we really need to get right to ensure reliability of results and patient protection? (Risk based thinking)

- Assumption: Likelihood of a successful, quality trial can be improved through prospective attention to preventing important errors that could undermine our ability to obtain meaningful information from a trial.

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Clinical Trials Transformation Initiative: QbD Project

- CTTI is a public-private partnership initiated to develop and drive adoption of practices that increase the quality and efficiency of clinical trials.
- More than 80 organizations from across clinical trial enterprise (regulators, industry, patient advocacy groups, professional societies, investigator groups, academic institutions)
- Identify best practices and develop methods and tools to apply principles of QbD to the scientific and operational design of clinical trials

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CTTI QbD Project – "Principles Document"

- Describes Critical to Quality (CTQ) factors generally relevant to most clinical trials
- Emphasizes that the criticality of different CTQ factors is based on the type and design of trial being conducted
- Emphasizes the importance of engaging all stakeholders in study development
- Emphasizes the importance of not falling into check list mentality, but use of interactive discussion when consider CTQ factors
- Provides considerations and example questions for each CTQ factor to spur cross-functional group discussion

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Principles Document – CTQ Factors

PROTOCOL DESIGN

- Eligibility Criteria
- Randomization
- Masking
- Types of Controls
- Data Quantity
- Endpoints
- Procedures Supporting Study Endpoints and Data Integrity
- Investigational Product (IP) Handling and Administration

FEASIBILITY

- Study and Site Feasibility
- Accrual

PATIENT SAFETY

- Informed Consent
- Withdrawal Criteria and Trial Participant Retention
- Signal Detection and Safety Reporting
- Data Monitoring Committee (DMC)/Stopping Rules (if applicable)

STUDY CONDUCT

- Training
- Data Recording and Reporting
- Data Monitoring and Management
- Statistical Analysis

STUDY REPORTING

- Dissemination of Study Results

THIRD-PARTY ENGAGEMENT

- Delegation of Sponsor Responsibilities
- Collaborations

https://www.ctti-clinicaltrials.org/projects/quality-design

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EMA Reflection Paper on Risk Based Quality Management in Clinical Trials


EUROPEAN MEDICINES AGENCY
SCIENCE · MEDICINES · HEALTH

Reflection paper on risk based quality management in clinical trials

Draft Agreed by the Clinical Trial Facilitation Group (CTFG) for release for consultation	31 May 2011
Draft Adopted by the Good Clinical Practice (GCP) Inspectors Working Group for consultation	14 June 2011
Start of public consultation	5 August 2011
End of consultation (deadline for comments)	15 February 2012
Agreed by the Clinical Trial Facilitation Group (CTFG) for publication	13 September 2012
Adopted by GCP Inspectors Working Group	13 September 2012
Keywords	Quality Management, Risk Management, Quality Tolerance Limit, Risk Control, Clinical Trial

- Overlap QbD and Risk Based Monitoring
- Describes key elements of quality system
- Development of systematic, prioritized, and risk-based approaches to management of clinical trials

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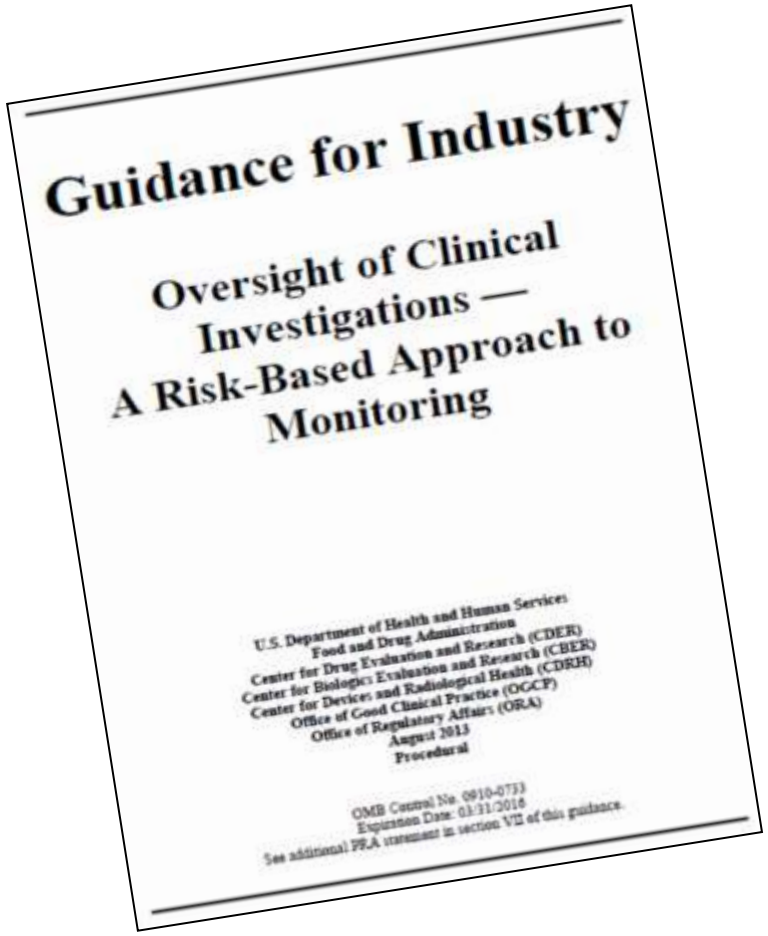
FDA Guidance on Monitoring



Guidance for Industry

Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Good Clinical Practice (OGCP)
Office of Regulatory Affairs (ORA)
August 2013
Procedural

OMB Control No. 0910-0733
Expiration Date: 03/31/2016
See additional PRA statement in section VII of this guidance.

- Quality is an overarching objective that must be built into the clinical trial.
- Emphasizes need for risk assessment to determine critical data and procedures that should be addressed in monitoring.
- Reminds that monitoring is a quality control tool for determining whether key or critical activities are being carried out as planned, so that deficiencies can be identified and corrected.

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Monitoring Plan Development - Important Considerations

- Complexity of study design/study procedures
- Types of study endpoints
- Clinical complexity of study population
- Geography where will be conducted
- Relative experience of clinical investigators
- Electronic data capture and other electronic systems
- Relative safety of investigational product
- Stage of the study
- Quantity of data

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Monitoring Plan Development - Important Considerations

- Discourages “One Size Fits All” approach to monitoring
- Encourages use of a variety of monitoring techniques
  - Centralized
  - Remote
  - On-site

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Final Thoughts
Successful Quality Management and Risk Based Approaches

- Maintain data integrity and the safety of trial participants (and patients in the post approval realm) within, and across, clinical development programs
- Make available beneficial new therapies for patients based on a foundation of high-quality evidence
- Improve efficiencies and optimize resource utilization (Industry, Regulators, Healthcare system)

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Challenge Questions

1. True or False? Only clinical trial data that is 100% accurate may be used by regulators to support regulatory decisions and product labelling.

   ANSWER: False

2. Quality by Design Principles emphasize which of the following?
   a) All CTQs are of equal importance in clinical studies.
   b) The CTTI Principles document should be used as a checklist to ensure you have at least touched on all CTQ factors when assessing your study.
   c) The importance of engaging all stakeholders when developing the study protocol

   ANSWER: c)

"Quality is never an accident; it is always the result of high intention, sincere effort, intelligent direction and skillful execution; it represents the wise choice of many alternatives"

- William A. Foster

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