

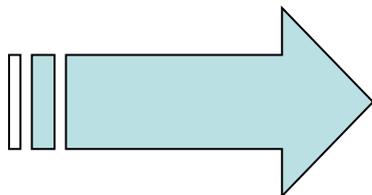


Quality Risk Management for Clinical Trials

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Current Challenges in Clinical Trial

- Expanding global footprint of trial conduct
 - Varying medical practice
 - Varying GCP experience of clinical investigators
- Increasing number of sites required for a given study
- Increased reliance on 3rd parties for trial conduct
- Expanded in-licensing and co-development agreements



Shared concerns about whether current trial oversight model is:

1. sustainable
2. effective



We have faced and addressed similar challenges in product manufacturing

PRIOR GMP CHALLENGES

Decreased inspectional capacity due to:

- Increased number of facilities
- Increased in foreign facilities
- Increase in number, diversity, and complexity of drugs and manufacturing processes

GMP DESIRED STATE

- Manufacturers have extensive knowledge about critical product and process parameters and quality attributes
- Manufacturers control process through quality systems over life cycle and strive for continuous improvement
- FDA Role: Initial verification, subsequent audit

Can we apply Quality by Design (QbD) to clinical trials?

- Systematic approach to development
- Begins with predefined objectives
- Emphasizes product and process understanding and process control
- Based on sound science and quality risk management

from ICH Q8(R1)



But, clinical trials are inherently variable systems with a goal of producing reliable data for regulatory decision-making . . .

How can this be reconciled with a quality system framework originating in mass manufacturing?

Systems approach works well for many processes

- Being applied in health care, service delivery, administrative processing
- Variety of tools and methods that can be selected for specific application
- We are exploring examples of use in scientific activities



What is Quality in a Clinical Trial Context ?

The ability to *effectively and efficiently* answer the intended question about the benefits and risks of a medical product (therapeutic or diagnostic) or procedure while assuring protection of human subjects.*

*Clinical Trials Transformation Initiative at: <http://www.trialstransformation.org/scope>



What is a Good Clinical Practice Quality System?

- A quality framework that extends across a drug's development lifecycle
- *Coordinated activities* that collectively permit sponsors and CROs to appropriately direct and control their clinical trials and clinical development programs in compliance with applicable statutes and regulations.

“PhRMA supports the concept that sponsors and CROs develop and employ an appropriate Quality Management System (QMS) to manage the overall clinical development process.”

PhRMA White Paper on Acceptable Approaches for Clinical Trial Monitoring, March 2009.

“Good Clinical Practice Quality Systems” permit companies to:

- Build quality into their clinical development programs
- Define controls to:
 - Prevent errors
 - Identify potential problems and intervene before issues become endemic
- Apply risk management principles to effectively target resources to activities that present a greater risk to data integrity and human subjects protection



GCP Quality Systems should focus on high risk activities that:

1. Underpin data quality and integrity
2. Ensure the integrity of conclusions drawn in a marketing application
3. Ensure human subject protections



Quality Systems

- Say what you do
- Do what you say
- Prove it
- Improve it



Say what you do

Governance

1. Sufficient resources for compliance and quality
2. Responsible, accountable individual(s)
3. Interdepartmental coordination and exchange of information for better decision-making

Policies, Procedures & Key Documents

- Prospectively define procedures and responsibilities for key clinical trial activities, **starting with protocol development**
- Address anticipated risks during process development



Do what you say

Training

Policies, procedures, study requirements, and responsibilities are communicated prospectively to affected company staff. CRO and service provider personnel, and Clinical Investigators



Prove it

Risk-based Monitoring

- Process Management
- Verify that critical activities, including Quality Control, are carried out as planned

Risk-based Auditing

- Process level evaluation

Trend analysis / metrics from monitoring & auditing

- Proactively identify and evaluate compliance signals
- Identify unanticipated risks

Monitoring

- Methods to proactively detect, assess, and remediate the root causes of clinical trial noncompliance in real-time
- Includes a range of Clinical Monitoring activities:
 - On-site monitoring focusing on key data and processes
 - Remote and central monitoring
 - Data Management metrics and trending
 - Statistical monitoring to assess data trends across sites and trials
 - Data mining
- Focus is more expansive than the Clinical Investigator
 - Incorporates monitoring of critical internal processes



Improve it

- Corrective and Preventive Actions
- Feedback and training
- Organizational learning



Closing Thoughts

We believe that:

1. Working together to define what constitute effective GCP quality systems, and
2. Aligning the Agency's inspection program with a quality systems model

will give industry greater predictability in FDA review and inspections while giving FDA the assurances it needs to successfully fulfill its mission.