Workshop on Quality Risk Management: Understanding What Matters

A Clinical Trials Transformation Initiative (CTTI)-hosted Meeting
September 20–21, 2012
Hyatt Regency Bethesda
One Bethesda Metro Center
7400 Wisconsin Ave., Bethesda, Maryland 20814

MEETING BACKGROUND

Current models for clinical trial design, implementation and oversight may have become outmoded and unsustainable in a global, complex clinical trial environment. In particular, existing oversight models, which generally rely on frequent, on-site monitoring visits by sponsor personnel, may not optimally address the most critical risks to trial integrity. A key conclusion of a Clinical Trials Transformation Initiative (CTTI) monitoring project was that clinical trial monitoring should be viewed as one component of an overall quality framework. Project participants, representing a broad cross-section of the clinical trials enterprise, agreed that widespread adoption of an enlightened "quality-by-design" approach to trial planning, conduct, and oversight is needed to ensure trial quality and efficiency. Such an approach would apply risk management principles to the design and execution of clinical trials.

Quality-by Design (QbD) emphasizes building quality into a process from the beginning and has been successfully applied in the manufacturing arena. Applied in clinical development, this approach would prospectively examine the design and objectives of trial and identify "critical to quality" factors (e.g. key data and trial processes such as randomization). Understanding what aspects of a trial are "critical to quality" is essential to subsequently identifying and managing important and likely risks to trial quality. These risks can be managed through modifying trial design, tailoring its implementation, and providing sensible, risk-based oversight.

Participants in an inaugural CTTI workshop on "Quality Risk Management: Making Clinical Trials Fit for Purpose" held in August 2011 explored principles of risk management and Quality-by-Design from other disciplines and examined how such principles could be adapted to enhance clinical trial design and execution. Participants generally agreed that these approaches have the potential to improve clinical trial efficiency while enabling sponsors and clinical investigators to meet their fundamental obligations to protect individuals who volunteer for research and to oversee their trials. In particular, these approaches reposition monitoring as one tool for ongoing evaluation and improvement. Focusing on critical aspects of a trial could also substantially reduce the burden of clinical trial conduct by relieving sponsors of a perceived obligation to mitigate every potential risk posed by a trial, especially for those activities that minimally affect data quality and human subject protection.

MEETING OBJECTIVES

- Develop understanding of risk-based Quality by Design for clinical trials of drug treatments, from general principles, real-world examples, and hypothetical case studies
- Gain confidence in the application of such concepts to clinical trials
- Identify obstacles to the adoption of this approach
- Identify opportunities for dissemination of these principles and practices to a broad array of stakeholders.

PARTICIPANTS

- Representatives from a broad cross-section of the clinical trial enterprise including regulators, government sponsors of clinical research, academia, industry, patient advocates, clinical investigators, and other interested parties
- Participants are expected to be actively engaged and dialogue both days

DAY 1 – SEPTEMBER 20, 2012

Meeting Co-chairs: Martin Landray (Oxford University)
Ann Meeker-O'Connell (CDER, FDA)
Briggs Morrison (Astra-Zeneca)

8:30 am WELCOMING REMARKS

8:30 – 8:40 am Opening remarks *Rob Califf*

8:40 am SESSION I: RATIONALE AND PRINCIPLES

Session Facilitator: Briggs Morrison

Objectives:

- Review the key drivers for quality (including the outcomes of previous CTTI activities)
- Discuss the principles and explain the jargon of Quality Risk Management and Quality by Design
- Review the regulatory perspective on methods to ensure quality in clinical trials

8:40 – 9:00 am What are the key drivers for quality?
Martin Landray

9:00 – 09:20 am Quality Risk Assessment and Quality by Design – principles not jargon
Briggs Morrison

9:20 – 9:40 am Regulatory requirements for ensuring quality: a US perspective
Ann Meeker O'Connell

9:40 – 10:00 am Regulatory requirements for ensuring quality: a European perspective
Fergus Sweeney

10:00 am BREAK

10:20 am SESSION II: PROVIDING GUIDANCE

Session Facilitator: Ann Meeker-O'Connell

Objectives:

- Review and discuss the Principles Document, and suggest further improvements

10:20 am – 12:00 pm Principles Document Review

12:00 pm LUNCH (PROVIDED)

12:45 pm SESSION III: REAL-WORLD EXAMPLES

Facilitator: Ann Meeker-O'Connell

Session Objectives:

- Review examples of clinical trials that have incorporated risk-based QbD approaches
- Discuss the advantages and the challenges of adopting this approach

12:45– 1:15 pm Example 1: A Study of Cardiovascular Events iN Diabetes (ASCEND) *Louise Bowman*

1:15 – 1:45 pm Example 2: "A case study of a clinical trial demonstrating a Quality by Design approach to Quality Risk Management" *Ken Sprenger*

1:45 – 2:00 pm Discussion

2:00 pm SESSION IV: BUILDING QUALITY IN TO A CLINICAL TRIAL CASE STUDIES – part I

Session Facilitator: Martin Landray

Session Objectives:

- Working in groups, participants will apply the Quality by Design principles to their hypothetical protocol outline, taking into account the concerns of key stakeholders.
- Define what matters for the trial, so called Critical to Quality (CTQ) parameters.
- Determine priority for addressing CTQ parameters.
- Explore the concepts of Quality by Design, including protocol design, trial operations, monitoring and quality improvement

2:00 – 2:15 pm Introduction to the working group activities *Martin Landray*

2:15 – 3:30 pm Workgroup activity: Review trial brief and develop risk assessment

Room A	Workgroup 1: Cardiology
Room B	Workgroup 2: Oncology
Room C	Workgroup 3: Mental Health
Room D	Workgroups 4: Cardiology
Room E	Workgroup 5: Oncology
Room F	Workgroup 6: Mental Health

3:30 pm BREAK

4:00 pm SESSION V: BUILDING QUALITY IN TO A CLINICAL TRIAL
CASE STUDIES – Feedback

Session Facilitator: *Briggs Morrison*

Session Objectives:

- Presentation and discussion of the approach to identifying "critical to quality" parameters taken by each workgroup
- Discussion of the challenges in adopting the principles
- Identification of likely obstacles (e.g. aspects where additional clarity required, anticipated issues in adopting such practice)

4:00 – 5:00 pm Each Workgroup Report out (10 minutes each)

5:00 – 5:30 pm Day 1 Wrap-Up: Review of the day's activity

Before leaving the room, participants must propose, in writing, each of the following:

- One suggestion for improvement of the Principles document.
- One aspect of identifying "critical to quality factors" that is challenging
- One component of the exercise that they will promote in their organization

6:00 pm RECEPTION

DAY 2 – September 21, 2012

8:30 am SESSION VI: BUILDING QUALITY IN TO CLINICAL TRIALS: CASE STUDIES – part II

Session Facilitator: *Martin Landray*

Session Objectives:

- Explore the role of risk management and monitoring in clinical trial design
- Considering those critical to quality parameters identified in Part I of the case study:
    - What proactive steps can be to avoid problems?
    - What ongoing checks can be performed to detect problems?
    - What level of error will trigger corrective actions?
    - How will corrective actions be formulated?
    - How will the impact of any corrective actions be assessed?
    - How will lessons be learned for the future?

8:30 – 8:50 am	Overview of approaches to Quality by Design Extension of the working group activities	*Martin Landray*

8:50 – 10:20 am Workgroup activity: Designing trial operations and monitoring approaches

Room A	Workgroup 1: Cardiology
Room B	Workgroup 2: Oncology
Room C	Workgroup 3: Mental Health
Room D	Workgroups 4: Cardiology
Room E	Workgroup 5: Oncology
Room F	Workgroup 6: Mental Health

10:20 am BREAK

10:40 am SESSION VII: REFLECTION AND IDENTIFICATION OF NEXT STEPS

Session Facilitator: Briggs Morrison

Session Objectives:

- Review and reflection (what worked, what didn't):
    - Principles document
    - Working group approach
    - Disseminating training within organizations
- Identify need for further training materials and approaches – what are practical steps to take
- Identify external barriers to widespread adoption of the risk-based Quality by Design approach. Who needs to be convinced and how would this best be achieved?

10:40 am – 12:15 pm Report out work group activity (5 min each group) and Interactive discussion/brainstorming (all attendees)

12:15 – 12:30 pm Closing remarks

12:30 – 1:30 pm BOXED LUNCH (PROVIDED)