



## **Workshop on Quality Risk Management: Understanding What Matters**

Executive Summary of Workshop held January 29-30, 2014

DoubleTree by Hilton Bethesda-Washington, DC, Bethesda, MD

**CTTI MISSION:** To identify and promote practices that will increase the quality and efficiency of clinical trials

*Workshop meeting materials, including agenda, participant list and presentations, are available on the Clinical Trials Transformation Initiative website at: <http://ctti-clinicaltrials.org/workshop-on-quality-risk-management-understanding-what-matters/>*

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## WORKSHOP BACKGROUND

Quality-by Design (QbD) emphasizes building quality into a process from the beginning. Applied in clinical development, this approach prospectively examines the design and objectives of trials and identifies “critical to quality” factors (CTQs). Understanding what aspects of a trial are “critical to quality” is essential to subsequently identifying and managing important and likely risks to trial quality.

Following an initial meeting exploring principles of risk management and QbD from other disciplines, and examining how such principles could be adapted to enhance clinical trial design and execution, a “principles document”, outlining high-level principles for building quality into trials, was developed. The CTTI Quality by Design Workshops Project - Critical to Quality Factors, referred to hereafter as the “principles document”, has been used in a series of workshops, allowing participants to practice applying these concepts through case studies.

Most recently, CTTI convened a working group (November 2013) to revise the principles document with the goal of creating a document that is more broadly applicable across all stakeholders.

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## WORKSHOP OBJECTIVES

The goal of the January 2014 session was to explore how QbD principles might be applied in practice with clinical trials of medical devices and diagnostics, drawing from real world examples and hypothetical case studies. The workshop objectives were to demonstrate some of the advantages of this approach, build confidence in its use, identify obstacles in its adoption, and highlight opportunities for dissemination of these principles and practices. Participants included a broad cross-section of stakeholders, including regulators, government sponsors of clinical research, representatives from academia and industry, patient advocates, and clinical investigators.

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## WORKSHOP SUMMARY

### Quality by Design – avoiding and addressing errors that matter

The workshop introduced a working definition of quality: “the absence of errors that matter to decision making”. “Errors that matter” have material impact on the protection of research participants or the ability to draw conclusions based on a trial’s data. The introductory session provided an overview of quality management and how it might be employed in clinical trials to prevent or minimize the opportunity for such errors. Key drivers of quality in a “good” clinical trial, defined as a trial that asks an important question and answers it reliably, were described. The session emphasized that the types of errors that matter may vary depending on trial design, the product under study, and other factors.

Ongoing attention to risk during trial progression, and sharing management plans and lessons learned, were also presented as important factors in overall trial quality.

Meeting participants then discussed the U.S. and European regulatory perspective on enhancing trial quality, and the differences between U.S. and European oversight and approval of medical devices. There was agreement between various stakeholders that application of QbD principles does not specify a particular type of protocol or methodology for trial oversight; they simply call for evidence of sufficient quality to support decision-making throughout a product's clinical development and use lifecycles. However, there may be reluctance from industry partners to use new methods due to an assumption that regulators won't support alternative methodology, causing delays or barriers to product approval. Regulators expressed planned focus on clinical trial reform and welcomed research sponsors to challenge the status quo. Participants agreed that communication in both directions is required during protocol development.

Subsequent presentations examined the medical device and diagnostics landscape from the academic, industry and payor perspectives, and how current issues are aligned with integration of QbD principles into practice. Recurrent themes emerged: 1) randomized clinical trials (RCTs) are the best method to eliminate bias, but trials should be fit for purpose, and well-conducted observational studies can provide valid answers to some questions, 2) key challenges extend from design through to execution, and attention should focus on pertinent research questions, suitable study designs, high-quality data, and appropriate statistical analyses, and 3) ensuring quality is key to bringing medical progress to patients.

Three examples of actual clinical trials that have incorporated QbD approaches were presented. These studies employed a risk-based approach to monitoring and/or progressive approaches to patient enrollment including registry-based models. Methods for obtaining quality data from registry-based trials were discussed, including database queries for event ascertainment, assuring reliable data sources, and including multiple layers of data.

The group then proceeded to discuss the principles document. The principles document is intended as a tool for inquiry in CTQs and associated risks. CTQs can be grouped into categories of feasibility, protocol design, patient safety, study conduct, study reporting and third-party service providers. The principles document asks questions to promote proactive, cross-functional discussions and critical thinking at the time of trial development about what is critical to quality for a specific trial, and about the events that might impede or facilitate achieving quality. The current draft has been revised to include device development focused inquiry, and expands the focus of questions to more explicitly consider perspectives of a broader group of stakeholders (patients, investigators, payers). It is not intended to be all-inclusive, serve as a checklist to be completed in isolation, or be a substitute for experience and critical thinking.

## Putting principles in to practice: A two-part exercise

Attendees then participated in a two-part exercise in which they were assigned to a cross-functional working group and tasked with applying QbD principles to a hypothetical protocol outline, taking into account the concerns of key stakeholders. Two groups addressed each of the 3 protocols, covering interventional cardiology, surgery, and diagnostics.

In Part I, the groups identified and then ranked factors that for their protocol would be critical to quality. Each group then presented their top five CTQ factors, including, their approach to identifying these factors and the challenges/obstacles they might encounter in adopting the QbD principles.

In Part II, the breakout groups took their top 5 CTQ factors from Part I, selected the 1 most important, and identified potential challenges to ensuring these aspects of the trial were successful, and developed risk-mitigation plans for each.

## Learning points

Themes for potential improvements to the principles document emerged during the discussion.

1. Attention to validity/importance of the research question should be augmented. Individuals involved in trial design and implementation should ask if the trial is asking a relevant question that needs to be answered. Many attendees thought that the principles document should include a way to evaluate the relevance of the research question, not only to the sponsor but also relative to other stakeholders (patients, clinicians, international parties).
2. Additional guidance should be provided about how the document can be used in real-world situations, including how it can be adapted to fit a specific therapeutic area or trial design.
3. Ease of use can be improved through formatting changes or development of an electronic application.
4. Include greater description of how site level personnel and patients can be involved in protocol development and conduct.

The most common challenge in using the CTQ factors is uncertainty about how to move from concept to practice. Participants sought additional information about best practices (who?, how?, when?) for real-world implementation. Participants also described the challenges related to risk prioritization in a multi-disciplinary team.

Several of the participants stated an intention to move their organization toward formal, cross-functional, risk-based review of study plans. Others indicated specific CTQs that might be most relevant in their own institutions. Others will seek to incorporate QbD elements into their existing workstreams and standard operating procedures, and improve patient advocacy in study development.

In summary, participants agreed upon some overarching principles:

- It is important to take time out in the early stages of protocol development to think through challenging issues and plan for quality.
- Convening a cross-functional team to engage in critical thinking about the protocol is key, and that teams may include but are not limited to:
  - Institutional departments
  - Clinical investigators
  - Patients
  - Other interested parties.
- The principles document outlines a range of common issues which should be considered and then applied appropriately to meet the specific needs of a particular study (not all CTQs apply in all situations).

### **Conclusion and Next Steps**

The workshop was well received by participants and was successful in demonstrating the advantages of a QbD approach in medical device and diagnostic trials. CTTI now plans to assess outcomes from previous workshops through qualitative case studies. Findings from that analysis, along with anecdotal evidence from the workshop series, will provide the foundation for further revision of the principles document, a publication describing the QbD methodology and principles document, and further dissemination of these concepts throughout the clinical trials enterprise.

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### **FUNDING STATEMENT**

Financial support for this project are provided by grant #U19 FD003800 from the U.S. Food and Drug Administration (FDA) and CTTI membership fees. In kind contribution of effort was provided by AstraZeneca, Janssen, Oxford University, Pfizer, FDA, and EMA. Additionally, Medtronic, the Health Disparities Research Consortium, and the National Organization for Rare Diseases made voluntary contributions to this workshop.

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### **ABOUT CTTI**

The Clinical Trials Transformation Initiative (CTTI) is a public-private partnership to identify and promote practices that will increase the quality and efficiency of clinical trials. The CTTI vision is a high quality clinical trial system that is patient-centered and efficient, enabling reliable and timely access to evidence-based prevention and treatment options.

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*For more information, contact the QbD & QRM Project Manager Annemarie Forrest at [Annemarie.Forrest@duke.edu](mailto:Annemarie.Forrest@duke.edu) or visit <http://www.ctti-clinicaltrials.org>.*

## Appendix A. Meeting/Workshop Agenda

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### DAY 1 – JANUARY 29, 2014

#### 8:30 am WELCOMING REMARKS

8:30 Introduction to the Clinical Trials Transformation Initiative  
*Pamela Tenaerts (CTTI)*

8:40 Opening Remarks  
*Christy Foreman (FDA/CDRH)*

#### 8:50 am SESSION I: LANDSCAPE, RATIONALE AND PRINCIPLES

*Facilitator: Martin Landray (Oxford)*

*Objectives:*

- *Review the current landscape of medical device development and approval*
- *Discuss the principles and review the key drivers for quality (including the outcomes of previous CTTI activities)*
- *Review US regulatory and European perspectives on methods to ensure quality in clinical trials*

8:50 Quality Risk Assessment and Quality by Design in Clinical Research  
*Martin Landray (Oxford)*

9:05 How US Regulatory Requirements Contribute to Study Quality  
*James Saviola (FDA/CDRH)*

9:20 European Perspective on Quality  
*Angeles Alonso Garcia (EMA)*

9:40 Current Issues in Device Development and Approval – Industry Perspective  
*Ted Lystig (Medtronic)*

10:00 Current Issues in Device Development and Approval – Academic Perspective  
*Laura Mauri (Brigham and Women’s Hospital)*

10:20 Payor Perspective on Quality  
*Louis Jacques (CMS)*

10:40 Discussion

#### 11:00 am BREAK

#### 11:15 am SESSION II: REAL-WORLD EXAMPLES

*Facilitator: Roxana Mehran (Mount Sinai)*

*Objectives:*

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

11:15 Example 1: CoreValve U.S Pivotal Trial  
Ted Lystig (Medtronic)

11:30 Example 2: TASTE: Thrombus Aspiration During ST-Segment Elevation Myocardial Infarction. A Multicenter, Prospective, Registry Based Randomized Clinical Trial  
Roxana Mehran (Mount Sinai)

11:45 Example 3: SAFE-PCI: The Study of Access Site for Enhancement of Percutaneous Coronary Intervention for Women  
Sunil Rao (Duke)

12:00 Discussion

**12:15 pm LUNCH (PROVIDED)**

**1:00 pm SESSION III: PROVIDING GUIDANCE**

Facilitator: Ann Meeker-O'Connell (Janssen)

Objective:

- Review and discuss the Principles Document, and suggest further improvements 1

1:00 Principles Document Review  
Ann Meeker-O'Connell (Janssen)

**2:00 pm SESSION IV: BUILDING QUALITY IN TO A CLINICAL TRIAL (CASE STUDIES – Part I)**

Facilitator: Jean Mulinde (FDA/CDER)

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.
- Characterize the applicability of the Quality by Design factors as high, medium, or low.
- Select the top 5 factors that are critical to the success and quality of the trial protocol and why they are important.
- Develop 3 priority recommendations to assure a successful and efficient trial.

2:00 Introduction to the Working Group Activities  
Jean Mulinde (FDA/CDER)

2:15 Workgroup Activity: Review trial brief and develop risk assessment  
Jasmine Workgroup 1: Interventional cardiology  
Juniper Workgroup 2: Interventional cardiology  
Lavendar Workgroup 3: Surgery

Lilac            Workgroup 4: Surgery  
Insight        Workgroup 5: Diagnostics  
Wisdom        Workgroup 6: Diagnostics

**3:30 pm        BREAK**

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

*Facilitator: Martin Landray (Oxford)*

*Objective:*

- *Presentation and discussion of the approach to identifying “critical to quality” parameters taken by each workgroup*  
*Characterize the applicability of the Quality by Design factors as high, medium, or low.*

4:00            Workgroups that used the same case study report, review similarities and differences between the 2 groups

4:30            Workgroup Report Out by Case Study Groups (10 Minutes/Case Study)

- How were the top 5 factors selected?
- What are the expected challenges in adopting the principles?
- What are the likely obstacles to adopting the principles?

5:00            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 – JANUARY 30, 2014**

**8:30 am        SESSION VI: BUILDING QUALITY IN TO CLINICAL TRIALS  
(CASE STUDIES – Part II)**

*Facilitator: Roxana Mehran (Mount Sinai)*

*Objectives:*

- *Explore the role of risk management and monitoring in clinical trial design*
- *Take the one most important critical to quality parameter identified in Part I of the case study and address the following:*
  - *What proactive steps can be taken to avoid problems (mitigation plan)?*
  - *What ongoing checks can be performed to detect problems?*
  - *What type of error will trigger corrective actions?*

- *Promote continuous improvement. Consider:*
  - *What steps can be taken to ensure that corrective and preventive actions remain focused on CTQ aspects of a trial, are sustainable, and efficient? (Avoid the need to add additional activity for the sake of adding activity and making more complex and the complexity leads to inability to implement and sustain)*
  - *What steps can be taken to ensure the corrective action stays focused on addressing errors that matter?*
  - *How will lessons learned be captured and communicated?*

8:30 Overview of Approaches to Quality by Design  
Roxana Mehran (Mount Sinai)

8:50 Workgroup Activity: Designing Trial Operations & Monitoring Approaches

Jasmine	Workgroup 1: Interventional cardiology
Juniper	Workgroup 2: Interventional cardiology
Lavendar	Workgroup 3: Surgery
Lilac	Workgroup 4: Surgery
Insight	Workgroup 5: Diagnostics
Wisdom	Workgroup 6: Diagnostics

**10:10 am BREAK**

**10:30 am SESSION II: REFLECTION AND IDENTIFICATION OF NEXT STEPS**

*Facilitator: John Alexander (Duke)*

*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?*

10:30 Workgroups that used the same case study report, review similarities and differences between the 2 groups

11:00 Workgroup Report out by case study groups (20 min per case study) and Interactive discussion/brainstorming (all attendees)

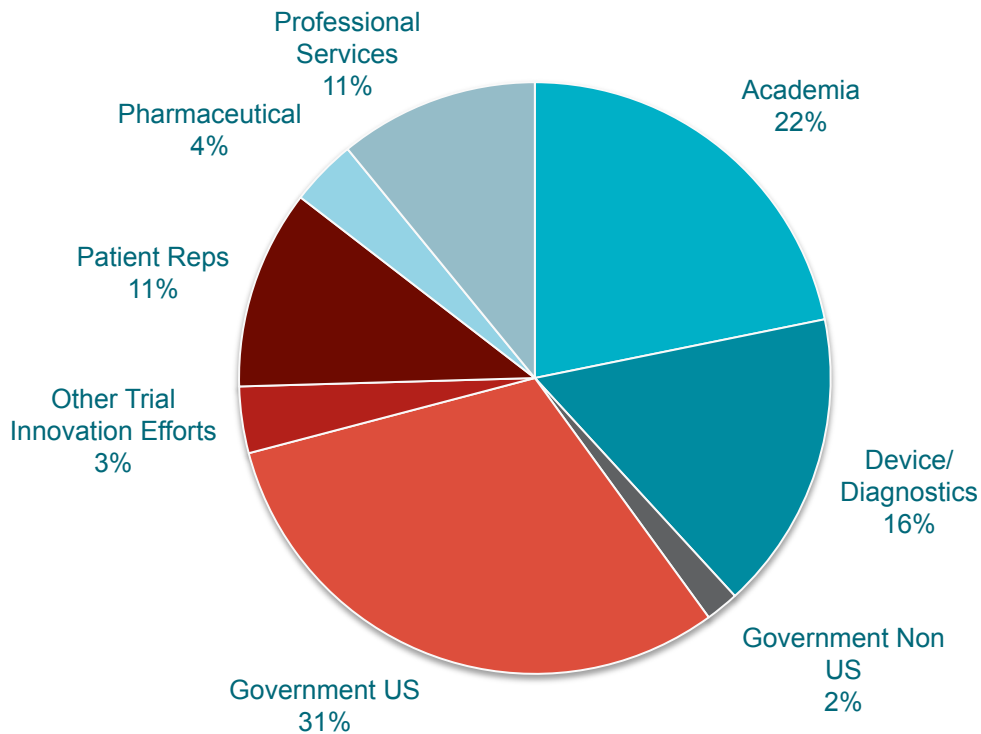
12:15 Closing remarks  
Pamela Tenaerts (CTTI), Karen Smith (PDF)

**12:30 pm ADJOURN**

## Appendix B. Workshop Participants

Our workshop participants include 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 in dialogue both days.

### STAKEHOLDERS REPRESENTED



### WORKSHOP CO-CHAIRS

Mark Behm (AstraZeneca)  
Diane Dorman (NORD)  
Martin Landray (Oxford University)  
Ted Lystig (Medtronic)

Ann Meeker-O'Connell (Janssen)  
Roxana Mehran (Mount Sinai)  
Jean Mulinde (FDA/CDER)  
Eric Richardson (FDA/CDRH)

### WORKSHOP ATTENDEES

Name	Affiliation
Alexander, John	Duke University
Alonso Garcia, Angeles	European Medicines Agency
Ashar, Binita	FDA/CDRH

Baldwin, Tim	NHLBI/NIH
Behm, Mark	Astra Zeneca
Breiter, David	Covidien
Brescher, Jessica	C.R. Bard, Inc.
Bulbulia, Richard	University of Oxford
Campbell, Robert	Children's Hospital of Philadelphia
Colder Carras, Michelle	Mental Health America
Collins, Doreen	Research Triangle Institute
Connor, Jason	Berry Consultants
Diaz, Roni	St. Jude Medical
Dorman, Diane	NORD
Foreman, Christy	FDA/CDRH
Gordon, Mary Jo (Telecon)	Patient Advocate
Guidry, Cyrus (Telecon)	Johnson & Johnson Global Surgery Group
Harper, Patricia	Becton Dickinson
Heller, Allen	Pharma Study Design LLC
Hieshetter, Janet	Dystonia Medical Research Foundation
Jacques, Louis	CMS
Jolly, Sanjit	Hamilton Health Sciences, McMaster University
Karpanek, Katharina (Telecon)	QM Company
Lam, Peter (Telecon)	Boston Scientific
Landray, Martin	University of Oxford
Laschinger, John	FDA/CDRH
Leitner, Angela	Regulatory & Clinical Research Institute, Inc.
Less, Joanne	FDA/OGCP
Lystig, Ted	Medtronic
Marinac-Dabic, Danica	FDA/CDRH
Mauri, Laura	Brigham and Women's Hospital
Meeker-O'Connell, Ann	Janssen
Mehran, Roxana	HDRC
Miller, Marissa	NIH/NHLBI
Mulinde, Jean	FDA/CDER
O'Callaghan, Katie	FDA/CDRH
Panhuis, Janette	Population Health Research Institute
Pina, Ileana	Montefiore
Pinnow, Ellen	FDA
Pocock, Stuart	London School of Hygiene & Tropical Medicine
Purohit-Sheth, Tejashri	FDA/CDRH
Rao, Sunil (Telecon)	Duke University
Reist, Craig	DCRI
Richardson, Eric	FDA/CDRH
Robb, Melissa	FDA/CDER
Rose, Daniel	Pulmonary Fibrosis Foundation
Saviola, James	FDA/CDRH
Shipman, Tamara	St Jude Medical
Smith, Karen	Parkinson's Disease Foundation

Stephenson, Betty  
Tcheng, Jimmy  
Themeles, Ellison  
Toth-Allen, Jean  
Wu, Winifred  
Zuckerman, Bram

Becton Dickinson  
Health Disparities Research Consortium  
PHRI  
FDA/OGCP  
Strategic Regulatory Partners, LLC  
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