Quality by Design: From Theory to Practice

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Senior Clinical Project Manager
Clinical Trials Transformation Initiative

February 23, 2016
Introduction to The Clinical Trials Transformation Initiative
To identify and promote practices that will increase the quality and efficiency of clinical trials

Public-Private Partnership
Co-founded by FDA and Duke University involving all stakeholders
80+ members
Collaboration Towards Solutions

Better Streamlined Fit for purpose Clinical Trials

Government and regulatory agencies
Industry: pharma bio device CRO
IRBs
Clinical investigators
Patients / Patient advocacy groups
Academia
Industry trade / Professional organizations
Clinical investigators

Patients / Patient advocacy groups

Academia
Industry trade / Professional organizations
CTTI Methodology

1. **State Problem**
   - Issue Statement, Project Plan

2. **Gather Evidence**
   - Literature Reviews, Multi-stakeholder Meetings, Surveys, Interviews

3. **Identify Gaps/BARRIERS**
   - Literature Reviews, Multi-stakeholder Meetings, Surveys, Interviews

4. **Analyze & Interpret Findings**
   - Team Meetings, Multi-stakeholder Meetings

5. **Refine Ideas**
   - Team Meetings, Multi-stakeholder Meetings

6. **Develop Recommendations/Tools**
   - Team Meetings, Multi-stakeholder Meetings

7. **Action**
   - Workshops, Pilot Studies, Measure Impact
## Portfolio of CTTI Projects

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<th>Closed Projects</th>
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Origins of CTTI’s Work on QbD

- Monitoring is not enough…
- 10% INDs fail to recruit a patient population appropriate to the intended use
- 3% of NDAs not approved due to missing critical data
- 25% of study procedures in phase 3 trials are not relevant to the assessment of primary endpoints
- Completed protocols across all phases average 2-3 amendments, 1/3 avoidable, all expensive
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Quality by Design: QbD Defined

“Quality” in clinical trials is defined as the absence of errors that matter

Prospectively examining the objectives of a trial and defining factors critical to meeting these objectives

... focusing effort on those “errors that matter” for the success of the clinical trial

... taking action to prevent important risks to these critical factors from negatively impacting outcomes

Understanding what data and processes underpin a successful trial is essential to subsequently identifying and managing important and likely risks to improve quality and outcomes for clinical trials

“Quality” in clinical trials is defined as the absence of errors that matter.

Error handling in clinical trials is critical, and QbD focuses on understanding and preventing these errors.
QbD Implementation: Plan, Do, Check, Act

**PLAN**
Build/plan quality into clinical trials from the beginning, focusing on what matters most

**DO**
Implement study risk management strategies

**CHECK**
Monitor leading indicators of quality in the study

**ACT**
Systematically drive remediation and learning
CTTI Quality by Design Project

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Critical to Quality Factors Principles Document

Questions to promote

- Proactive, cross-functional discussions
- Critical thinking at the time of trial development
- What is critical to quality for a specific trial
- Events that might impede or facilitate achieving quality

Not intended to serve as a

- “Tick the box” exercise
- “Checklist” to be completed in isolation
- Substitute for experience and critical thinking
- Quantitative risk assessment methodology

Not all-inclusive
Exploring the Critical to Quality Factors

http://www.ctti-clinicaltrials.org/toolkit/QbD
Exploring the Critical to Quality Factors

http://www.ctti-clinicaltrials.org/toolkit/QbD
PROTOCOL DESIGN

Eligibility Criteria
Randomization
Masking
Types of Controls
Data Quantity
Endpoints
Procedures Supporting StudyEndpoints and Data Integrity
Investigational Product (IP) Handling and Administration
Endpoints
Clearly defining study endpoints and describing how endpoint data are to be collected and reported will support consistent trial implementation across sites and prevent errors that may interfere with analysis and bring into question study conclusions. In defining endpoints, prospective attention should be given to the degree of objectivity in assessment of endpoints, the potential for simple external verification (e.g., death certificates, central and/or bioanalytical laboratory data), and potential for unbiased adjudication or review of endpoint data.

1. Is/are the endpoint(s) commensurate with the scientific question/objectives of the study?
2. Will the endpoint have a clinically meaningful impact on patient care or provide a unique building block for future research?
3. Are standardized and generally accepted endpoint definitions and methods to ascertain endpoints available?
4. If there are multiple primary endpoints, verify and describe how each is necessary to address/directly link to the scientific question posed by the study.
5. Consider the characteristics of the primary endpoint(s), including
   - How is the endpoint defined?
   - Is it assessable?
If you must call it a checklist…

“A set of checks to ensure the … critical stuff is not overlooked”

“Another set of checks to ensure people talk and coordinate and accept responsibility while nonetheless being left with the power to manage the nuances and unpredictabilities…”
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<th>Facilitator</th>
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<tbody>
<tr>
<td>[15 minutes]</td>
<td><strong>WELCOME AND INTRODUCTIONS</strong></td>
<td>All</td>
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<tr>
<td>[45 minutes]</td>
<td><strong>CLINICAL QBD RATIONALE AND PRINCIPLES</strong></td>
<td>Facilitator</td>
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<tr>
<td></td>
<td>Review the key drivers for quality in clinical trials</td>
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<td></td>
<td>Discuss the CTTI Quality by Design Project</td>
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<td>Review the regulatory perspective on methods to build</td>
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<td>quality into trial design</td>
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<tr>
<td>[45 minutes]</td>
<td><strong>PRINCIPLES DOCUMENT REVIEW</strong></td>
<td>Facilitator</td>
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<tr>
<td>[30 minutes]</td>
<td><strong>REAL-LIFE WORLD EXAMPLE</strong></td>
<td>Facilitator</td>
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<td>Review examples of clinical trials that have incorporated</td>
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<td>risk-based QbD approaches</td>
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<td>Discuss the advantages and the challenges of adopting this</td>
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<td>Working in groups, participants will apply the Quality by Design principles to the hypothetical protocol outline, taking into account the concerns of key stakeholders. Each group will select the top 5 factors that are critical to the success and quality of the trial and describe why they are important.</td>
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<td>[Plan for 15 minutes per group]</td>
<td>BREAKOUT SESSION 1 – GROUP REPORT OUT</td>
<td>Workgroup feedback: Present and discuss the approach to identifying “critical to quality” parameters taken by each workgroup (15 minutes each)</td>
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<td>[60 minutes]</td>
<td>BREAKOUT SESSION 2</td>
<td>Select one critical to quality parameter identified in the previous breakout session and address the following: • What are the risks related to this critical to quality parameter? • What proactive steps can be taken to avoid problems? • What ongoing checks can be performed to detect problems? • What type of error will trigger corrective actions? • How will lessons learned be captured and communicated?</td>
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<td>30 minutes</td>
<td>IMPLEMENTATION</td>
<td>1. Review CTTI toolkit 2. Discuss any barriers to widespread adoption of the QbD approach within [ ] and identify actions to address these barriers.</td>
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<td>15 minutes</td>
<td>NEXT STEPS AND CLOSING REMARKS</td>
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| 30 minutes | **IMPLEMENTATION**  
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2. Discuss any barriers to widespread adoption of the QbD approach within [] and identify actions to address these barriers. | Facilitator All |
| 15 minutes | **NEXT STEPS AND CLOSING REMARKS** | Facilitator |

**BUILDING QUALITY IN TO A CLINICAL TRIAL - CASE STUDY: BREAKOUT SESSION 1**

Working in groups, participants will apply the Quality by Design principles to the hypothetical protocol outline, taking into account the concerns of key stakeholders. Each group will select the top 5 factors that are critical to the success and quality of the trial and describe why they are important.

- What proactive steps can be taken to avoid problems?
- What ongoing checks can be performed to detect problems?
- What type of error will trigger corrective actions?
- How will lessons learned be captured and communicated?
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Proposed Agenda for a daylong Workshop. May be split across multiple days depending on attendee availability. Include sufficient time in each Session for Q&A / group discussion.
CTTI Quality by Design Project

- Produce a draft document outlining principles for building quality into the design and operations of trials
- Test and refine the document through a series of workshops
- Evaluate the workshops’ impact
- Encourage and support implementation through development of appropriate resources
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CTTI Quality by Design Recommendations

“Quality” is defined as the absence of errors that matter to decision making—that is, errors which have a meaningful impact on the safety of trial participants or credibility of the results (and thereby the care of future patients)

- Create a culture that values and rewards critical thinking and open dialogue about quality, and that goes beyond sole reliance on tools and checklists

- Focus effort on activities that are essential to the credibility of the study outcomes

- Involve the broad range of stakeholders in protocol development and discussions around study quality

- Prospectively identify and periodically review the critical to quality factors
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Sustaining Clinical Quality-by-Design Requires A Quality Culture

Essential Components of a Quality Culture

**Leadership**
(Managers know Quality is a priority; Empowerment)

**Processes & Behaviors**
(Employees know their role and responsibilities)

**Learning & Knowledge Sharing**
(Knowledge is constantly changing; learning from peers)

**Values**
(Employees understand and are driven by their connection to the patient)

“Organizational learning is a process of detecting and correcting error.”
- Chris Argyris

Coleen Glessner, Alexion, *Operationalizing QbD in Clinical Trials*, October 2014
CTTI Quality by Design Recommendations

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THINK about the protocol

• What is the rationale for...
  – Choice of study population
  – Sample size
  – Inclusion/exclusion criteria
  – Data items collected
  – Practical procedures and assessments
  – Biochemical assays
  – Study endpoints

• Just because you can ... doesn’t mean you should...

Louise Bowman, University of Oxford, *Operationalizing QbD in Clinical Trials*, April 2015
You start out with a beautiful green tree that should be admired and then everybody in the family wants to put an ornament on it... and no one will take grandma’s ornament off the tree. So you end up with a protocol that is impossible to do and is very distracted from answering the question you originally had.

- Dr. Robert Califf, Mind the Gap seminar, “Innovative Approaches to Clinical Trials.”
CTTI Quality by Design Recommendations

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QbD at MDCO

1. Identify what matters, eliminate the rest
   - Trial design
   - Data collection
   - Study management
   - Site selection & management

2. Identify meaningful risks to key objectives
   - What can go wrong?
   - How will we know?
   - What can we do about it?

3. Control risks
   - Plan action to reduce error

4. Monitor performance
   - Quality indicators aligned with trial objectives

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CTTI Quality by Design Toolkit

Learn About QbD
Introduce QbD
Adopt QbD

QbD (Quality By Design) Toolkit

Quality by Design in clinical trials may be defined as the absence of errors that matter to decision making (i.e., errors that have a meaningful impact on patient safety or interpretation of results). The CTTI QbD project team, made up of stakeholders from across the clinical trials enterprise, has held workshops, developed resources, and issued recommendations to encourage the adoption of QbD. This web-based QbD Toolkit provides additional resources for facilitating adoption and real world application of QbD concepts.

What is this QbD Toolkit?

Mark Behm from Astra Zeneca describes the QbD Toolkit and how you and your organization can use it to learn about and implement QbD.

http://www.ctti-clinicaltrials.org/toolkit/QbD
Learn About Quality by Design

Learn About QbD

Defining QbD

This section of the Toolkit provides an introduction to QbD through videos, downloadable presentations, and peer-reviewed articles. Learn about QbD and why it matters in clinical trials. Leverage these tools to teach others in your organization about QbD in order to secure their interest and support. Watch Martin Landray from University of Oxford describe Quality by Design.

CTTI's QbD Recommendations

The CTTI QbD project has produced recommendations on the use and implementation of QbD.

PowerPoint describing QbD

This PowerPoint Slide presentation provides an overview of QbD. It can be downloaded and used to teach your team about QbD.

QbD Publication in DIJ

This publication, Clinical Trials: Rethinking How We Ensure Quality, by Landray, et al. in Drug Information Journal 46(6) 657-660, provides an overview of QbD in Clinical Trials.

http://www.ctti-clinicaltrials.org/toolkit/QbD
Introduce Quality by Design

Introduce QbD to Your Team

QbD is about prospectively examining the objectives of a clinical trial and defining those factors that are critical to meeting those objectives. This requires thinking differently about clinical trials. In order to do that effectively, we have provided tools below to help introduce your team to QbD concepts and how they apply in clinical trials. The sections include: understanding QbD; exploring critical to quality factors (CTQs) through the QbD Principles Document; and applying QbD through workshop tools.

Understanding QbD?
For this component, reference the earlier section in the Toolkit on Learn about QbD. You can also review CTTI's QbD Recommendations.

QbD Principles Document
The Principles Document can be used 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.

Workshop Tools
Hold a workshop to educate attendees about QbD and how to apply the QbD principles through hands-on exercises during breakout sessions. Case studies, facilitator tips, and presentation slide templates are provided. You can also leverage the past CTTI QbD workshop materials.

http://www.ctti-clinicaltrials.org/toolkit/QbD
Introduce Quality by Design

**Workshop Tools**

Tools for hosting a QbD workshop within your own organization are provided. This includes case studies and a facilitation guide to educate attendees about clinical QbD and how to apply the QbD principles through hands-on exercises during breakout sessions. In addition, PowerPoint slide decks are provided as templates to build your own workshop. Past CTTI QbD workshop materials also are good resources.

- Model Agenda for a QbD Workshop
- CTTI's QbD Workshop Template Deck
- QbD Workshop Facilitator Tips

[http://www.ctti-clinicaltrials.org/toolkit/QbD](http://www.ctti-clinicaltrials.org/toolkit/QbD)
Adopting Quality by Design

Get Started
This section provides insights for getting started and securing buy in within your organization.

Introduce QbD to Your Team
Leverage our tools provided in the sections: Learn about QbD and Introduce QbD to begin QbD discussions within your organization.

Implement
Adopting QbD take time and effort. In this section, we share tips and insights from others that have implemented QbD to help you in the process.

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Adopting Quality by Design

Perspectives & Champions
CTTI shares considerations for internal and external champions.

Components for QbD Adoption
This resource describes the four key components needed for QbD adoption.

Setting Expectations
Setting expectations is essential for success. We provide some insights from others that have implemented QbD.

Measurement
Our CTTI QbD team recommends the iterative "Plan-Do-Check-Act" approach to measurement. Recommendations on how to employ that approach are provided.

Team Recognition
Recognizing the internal team that is championing QbD in your organization is a key to success. Our helpful hints for team recognition are included.

http://www.ctti-clinicaltrials.org/toolkit/QbD
Resources

www.ctti-clinicaltrials.org → “What We Do”

- CTTI Quality by Design Project
  - Project overview
  - Recommendations
  - Webinars
  - Principles Document

- Quality by Design Toolkit

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Thank you.