Clinical Quality-by-Design (QbD): Principles to Practice

August 21, 2015
Disclaimer

The views and opinions expressed in this presentation are those of the individual presenters and do not necessarily reflect the views of the Clinical Trials Transformation Initiative.
Agenda

- Introduction to CTTI and the Quality by Design Project
  Ann Meeker-O’Connell, Head, Risk Management & External Engagement Bioresearch Quality and Compliance, Johnson & Johnson

- Quality by Design Project Recommendations and Implementation Toolkit
  Mark Behm, Senior Director Quality Assurance, AstraZeneca

- Q & A
Introduction to CTTI
Clinical trials in crisis

The changing structure of industry-sponsored clinical research: pioneering data sharing and transparency.

Kuntz RE.
Addressing This Need

To identify and promote practices that will increase the quality and efficiency of clinical trials

Public-Private Partnership
Co-founded by Duke University and FDA involving all stakeholders
70+ 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
CTTI Methodology

State Problem

Identify Research Impediments
Issue Statement, Project Plan

Gather Evidence

Identify Gaps/Barriers
Literature Reviews, Multi-stakeholder Meetings, Surveys, Interviews

Find Solution

Analyze & Interpret Findings
Team Meetings, Multi-stakeholder Meetings

Refine Ideas

Develop Recommendations/Tools
Team Meetings, Multi-stakeholder Meetings

Action

Disseminate & Implement
Workshops, Pilot Studies, Measure Impact
# Portfolio of CTTI Projects

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<th>Investigational Plan</th>
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| **Closed Projects** | • Large simple trials  
  • Uses of electronic data                                                                 | • Central IRB  
  • Site metrics  
  • Central IRB advancement  
  • GCP training                                             | • Adverse event reporting  
  • IND safety  
  • Monitoring                                                     |                                                        | • Long-term opioid data                                        |
| **Ongoing Projects**    | • Mobile clinical trials (program)  
  • Patient groups & clinical trials  
  • Pregnancy testing  
  • QbD  
  • Trials based on registries  
  • Uses of electronic data application | • Informed consent  
  • Investigator turnover  
  • Recruitment                                                       | • IND safety advancement  
  • Safety case studies                                              |                                                        | • Pediatric antibiotic trials  
  • Streamlining HABP/VABP trials  
  • Unmet need in antibiotic development  
  • ABDD pilot                                                      |
Thank you to our team…

- Mark Behm (Astra Zeneca)
- Coleen Glessner (Alexion Pharmaceuticals)
- Martin Landray (University of Oxford)
- Ann Meeker-O’Connell (Johnson & Johnson)
- Briggs Morrison (Syndax Pharmaceuticals)
- Jean Mulinde (FDA/CDER)
- Nancy Roach (Fight Colorectal Cancer)
- Stephanie Shapley (FDA/CDER)
- Fergus Sweeney (EMA)

…and the many other project contributors who have given their time and effort to make this project a success!
CTTI Quality by Design Project Overview
Key Challenges in Clinical Development

**Trial design**
- Complexity
- Feasibility
- Delays from avoidable amendments

**Trial oversight**
- Over-reliance on retrospective oversight methods
- Focus on the accuracy of single data points
- One size-fits-all approach

**Salvage vs. prevention**

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.”
Addressing this challenge: Applying Quality-By-Design Concepts

General principles about what really matters in clinical trials can and should be developed

- That is, what do we really need to get right to ensure reliability of results and patient protection?
“Quality” in clinical trials is defined as the absence of errors that matter to decision-making.

- 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.
CTTI QbD Project Overview

- Produce a draft document outlining:
  - High-level principles for building quality into the design and operations of trials
  - One potential approach to prospective quality planning

- Test and refine the document through a series of workshops
  - Different therapeutic areas and product types
  - Model cross-functional dialogue, including input from investigators, patients, health authorities and others with a stake in trial conduct

- Evaluate the workshops’ impact and disseminate the initial results

- Encourage and support further development and implementation
Key Challenges Identified via Workshop Evaluation

**Moving From Principles to Practice**

Participants and their organizations believe in QbD
They were convinced that it was a better way to manage clinical trials
However, moving from understanding QbD to doing QbD was a key challenge

**Cultural Barriers**

Nearly all participants reported cultural barriers, especially:

- Fear of change
- Difficulty overcoming organizational inertia
- Lack of understanding for the value of QbD
- Concern it would take more time and create more work
Implementation: Our Response

Need:
- Participants wanted more examples of how others had implemented QbD in their clinical development programs

Supporting Materials:
- Three-part webinar series exploring concrete examples of real-world application of QbD Principles

Implementation: Our Response

Need:
- Participants wanted the QbD Principles to be finalized and published

Supporting materials:
- Publication developed including
  1) CTTI Recommendations,
  2) Appendix with updated Principles Document
Quality by Design Project 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

- Encourage proactive dialogue about what is critical to quality for a particular trial or development program and, when needed, the development of innovative methods for ensuring quality.

- Discourage overreliance on checklists and inflexible “one size fits all” approaches that undermine creation of specific strategies and actions intended to effectively and efficiently support quality in a given study.

- Verify that quality and performance measures are aligned with incentives driving a culture that rewards critical thinking.
Focus effort on activities that are essential to the credibility of the study outcomes

- Rigorously evaluate study design to verify that planned activities and data collection are essential.
- Streamline trial design wherever feasible.
- Deploy resources to identify and prevent or control errors that matter in the study.
- Consider whether nonessential activities may be eliminated from the study to simplify conduct, improve trial efficiency, and target resources to most critical areas.
Involve the broad range of stakeholders in protocol development and discussions around study quality

- Engaging all stakeholders with study development is an important feature of quality by design.

- The process of building quality into the study plan may be informed not only by the sponsor organization but also by participation of those directly involved in successful completion of the study such as clinical investigators, study coordinators and other site staff, and patients.

- Clinical investigators and potential trial participants have valuable insights into the feasibility of enrolling patients who meet proposed eligibility criteria, whether scheduled study visits and procedures may be overly burdensome and lead to early dropouts, and the general relevance of study endpoints to the targeted patient population.

- When a study has novel features in elements considered critical to quality (e.g., defining patient populations, procedures, or endpoints), early engagement with regulators should also be considered.
Prospectively identify and periodically review the critical to quality factors

The CTTI Quality by Design Principles can be used to identify those aspects in each study that are critical to generating reliable data and providing appropriate protections for research participants, and to develop strategies and actions to effectively and efficiently support quality in these critical areas.

Periodically review critical to quality factors to determine whether adjustments to risk control mechanisms are needed.
Implementation Toolkit
Implementation: Our Response

Need:

- Participants asked for resources to support establishing and sustaining QbD within their organizations

Supporting materials:

CTTI announces the launch of a new web based portal:
“Quality by Design Toolkit”

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

- Toolkit provides additional resources for facilitating adoption and real-world application of QbD

- Toolkit provides resources for those learning about QbD concepts and those ready to implement QbD into a clinical trial

- The web-based QbD Toolkit includes:
  - Overview of QbD Concepts,
  - Tools for educating your organization about QbD and its use,
  - Tools for implementation of QbD in a clinical trial, and
  - Interactive QbD Principles Document

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

Learn About 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 DJ

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
Teach Others About QbD

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.
Toolkit: 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](http://www.ctti-clinicaltrials.org/toolkit/QbD) also are good resources.

Model Agenda for a QbD Workshop

CTTI's QbD Workshop Template Deck

QbD Workshop Facilitator Tips
Toolkit: Adopting Quality by Design

Adopt QbD

Understanding QbD is just the beginning. The real impact will occur when QbD is implemented at your organization as part of your fundamental approach to clinical trial design and operationalization. To support you in the work of adopting QbD, we have provided guidance to get started, introduce QbD to your team, and implement QbD. Watch as Coleen Glessner shares her insights on the benefits of thinking differently with QbD.

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.

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

- View the Toolkit at [http://www.ctti-clinicaltrials.org/toolkit/QbD](http://www.ctti-clinicaltrials.org/toolkit/QbD)


- To view recordings of previous webinars from the CTTI-hosted webinar series, and general CTTI QbD resources visit [http://www.ctti-clinicaltrials.org/what-we-do/investigational-plan/qbd-qrm/products](http://www.ctti-clinicaltrials.org/what-we-do/investigational-plan/qbd-qrm/products)

- If you would like to be added to CTTI's Quality by Design e-mailing list, please contact Kimberley Smith at [kimberley.i.smith@duke.edu](mailto:kimberley.i.smith@duke.edu)

- Find additional CTTI resources on our website, [www.ctti-clinicaltrials.org](http://www.ctti-clinicaltrials.org)
Thank you.

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