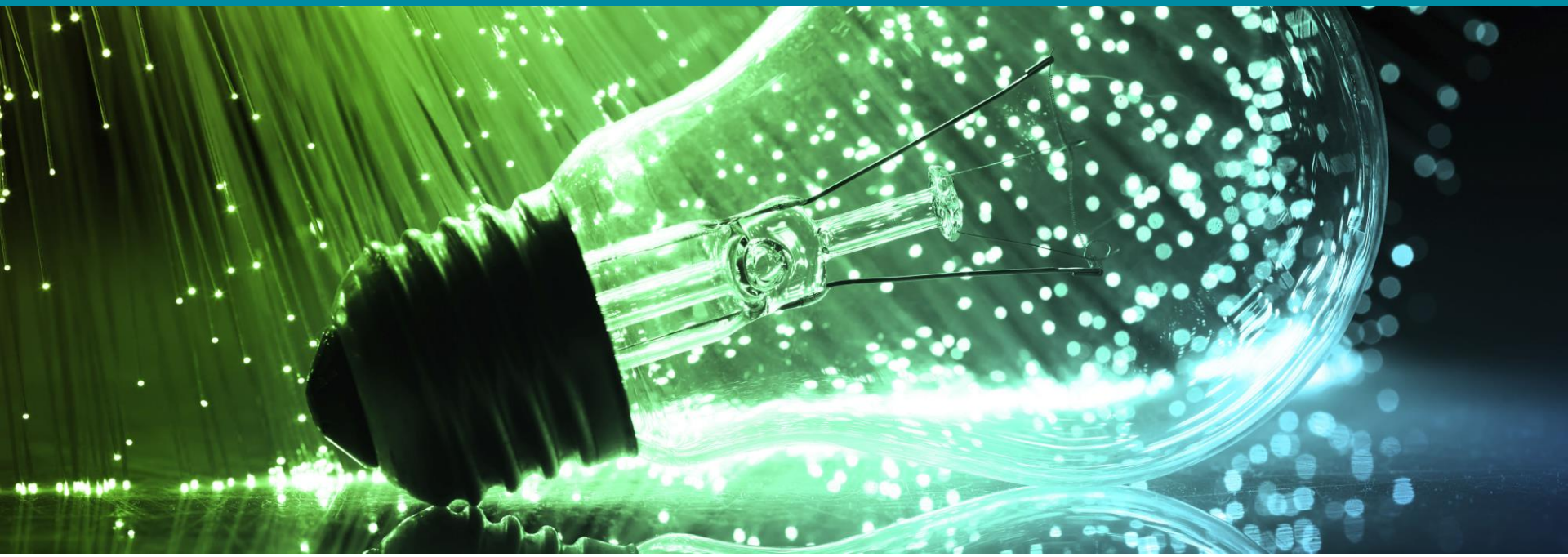
Clinical Quality-by-Design (QbD): Principles to Practice

August 21, 2015

CLINICAL
TRIALS
TRANSFORMATION
INITIATIVE



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

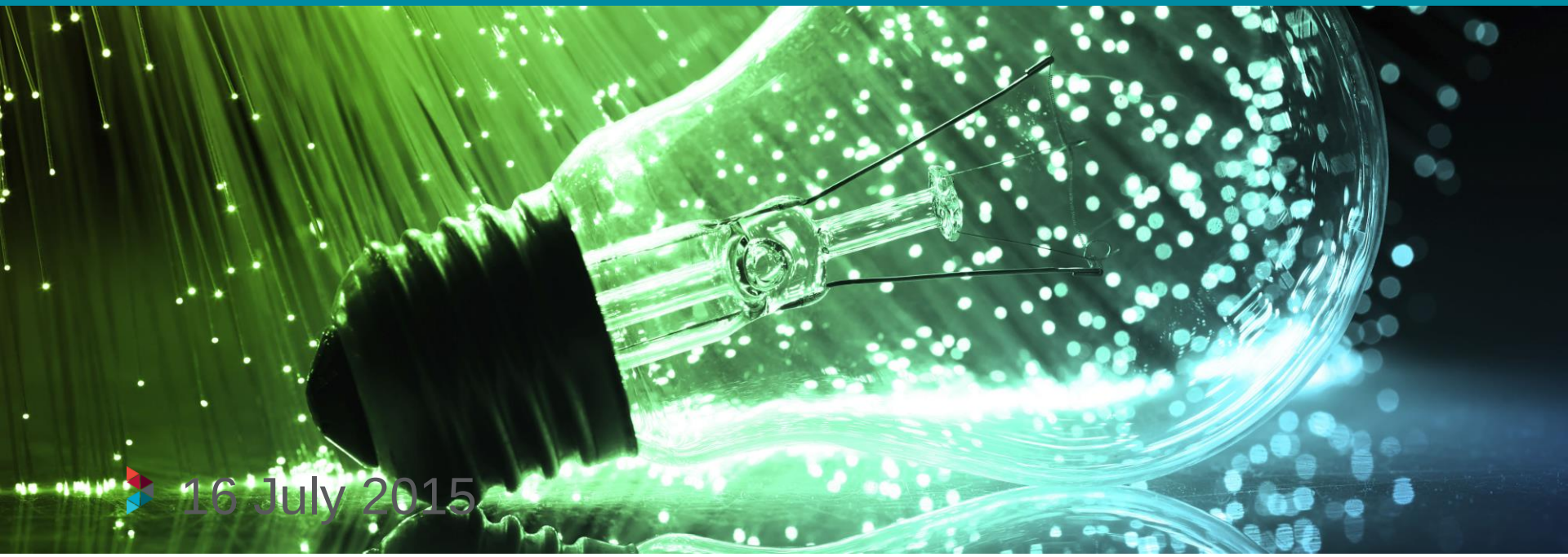
- Introduction to CTTI and the Quality by Design Project

  Ann Meeker-O'Connell, Head, Risk Management & External Engagement Bioresearch Quality and Compliance, Johnson & Johnson

- Quality by Design Project Recommendations and Implementation Toolkit

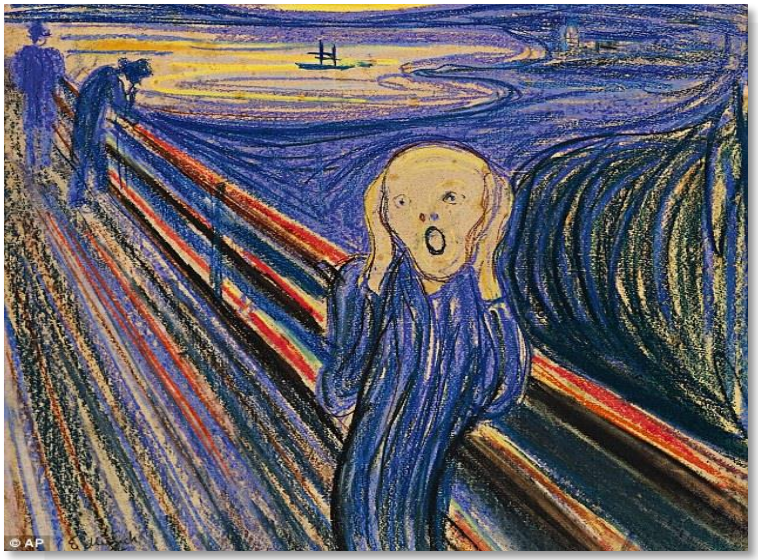
  Mark Behm, Senior Director Quality Assurance, AstraZeneca

- Q & A



Introduction to CTTI

Clinical trials in crisis

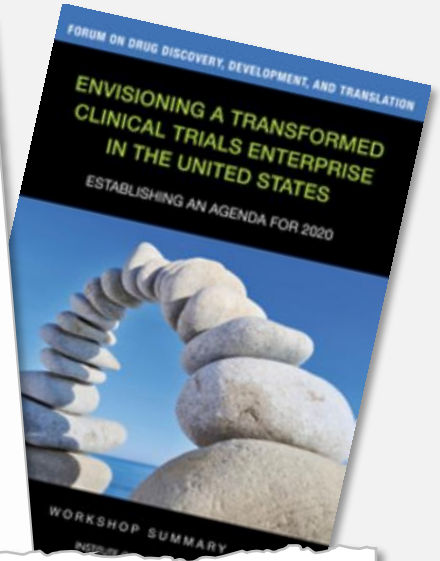


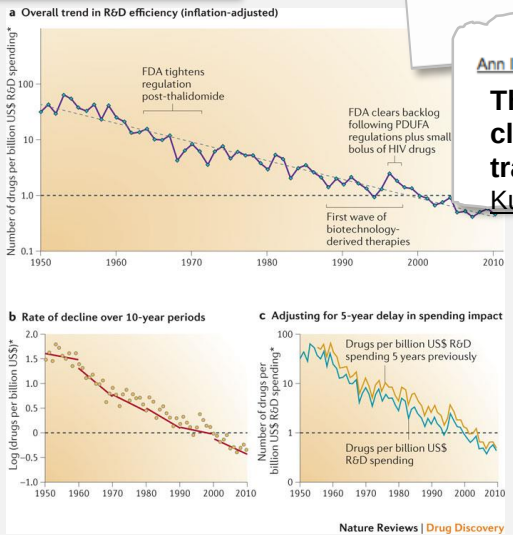
REPORT TO THE PRESIDENT

TRANSFORMATION AND OPPORTUNITY: THE FUTURE OF THE U.S. RESEARCH ENTERPRISE

Executive Office of the President
President's Council of Advisors on Science and Technology

NOVEMBER 2012





Ann Intern Med. 2013 Jun 18;158(12):914-5. doi: 10.7326/0003-4819-158-12-201306180-00011.

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

Kunt

BROOKINGS

RESEARCH | EVENTS | EXPERTS | ABOUT

MAR 5

PAST EVENT

Biomedical Innovation: Identifying Challenges and Prioritizing Needs

Addressing This Need

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 Duke University and FDA
involving all stakeholders
70+ members

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Collaboration Towards Solutions

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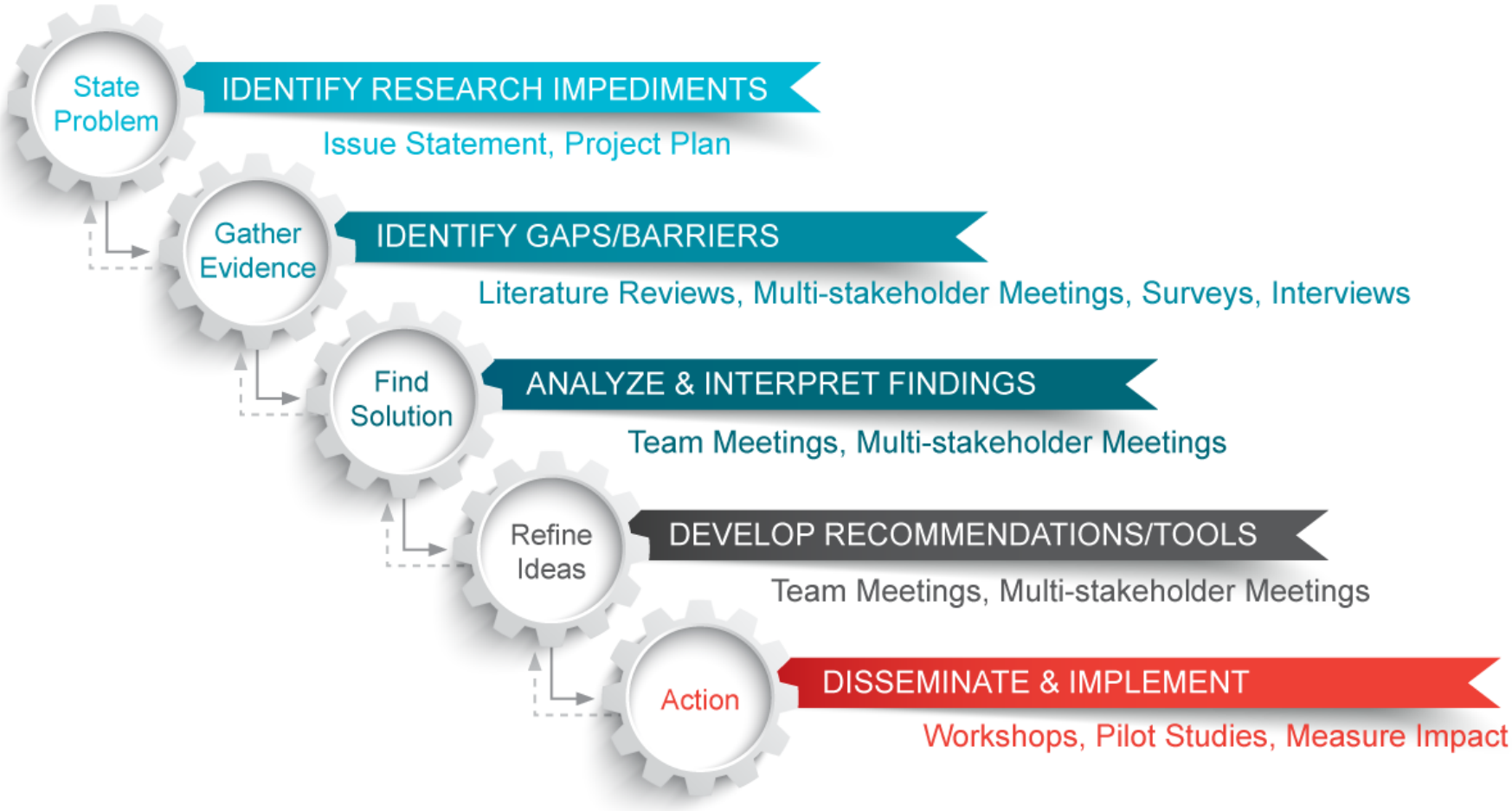
CTTI Methodology



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Portfolio of CTTI Projects

	Investigational Plan	Study Start-up	Study Conduct	Analysis & Dissemination	Specialty Areas
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	• State of clinical trials • DMCs	• 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!

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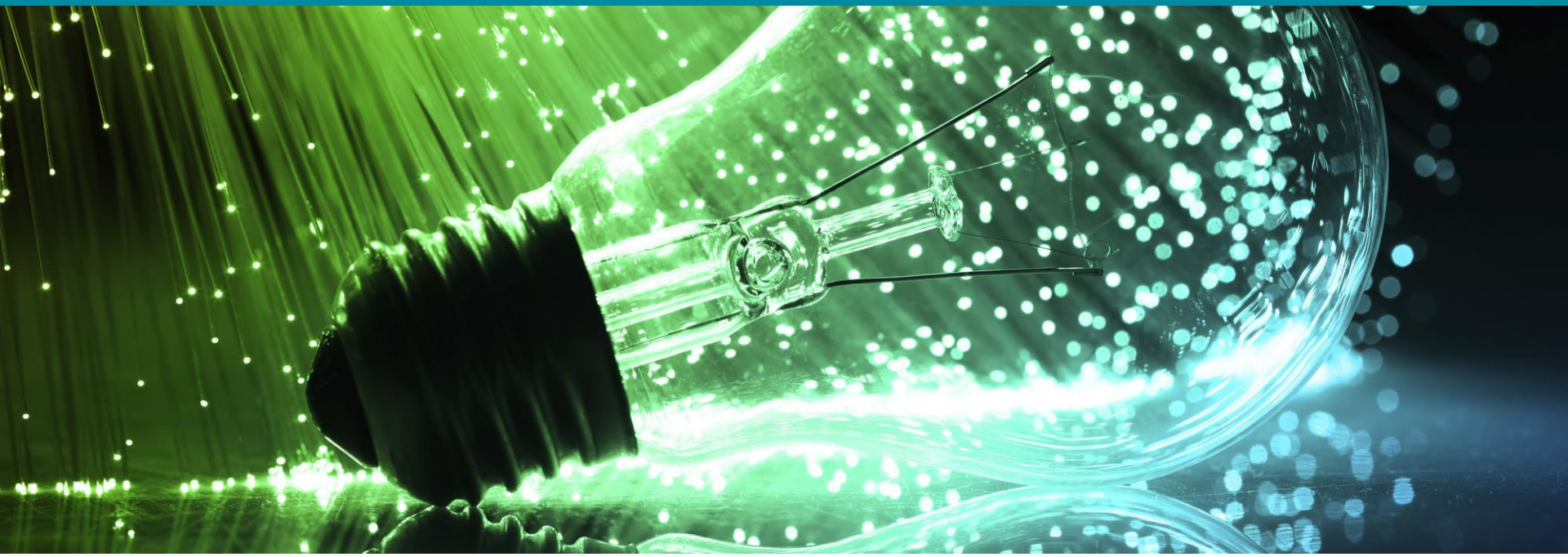

CTTI Quality by Design Project Overview

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."

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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?

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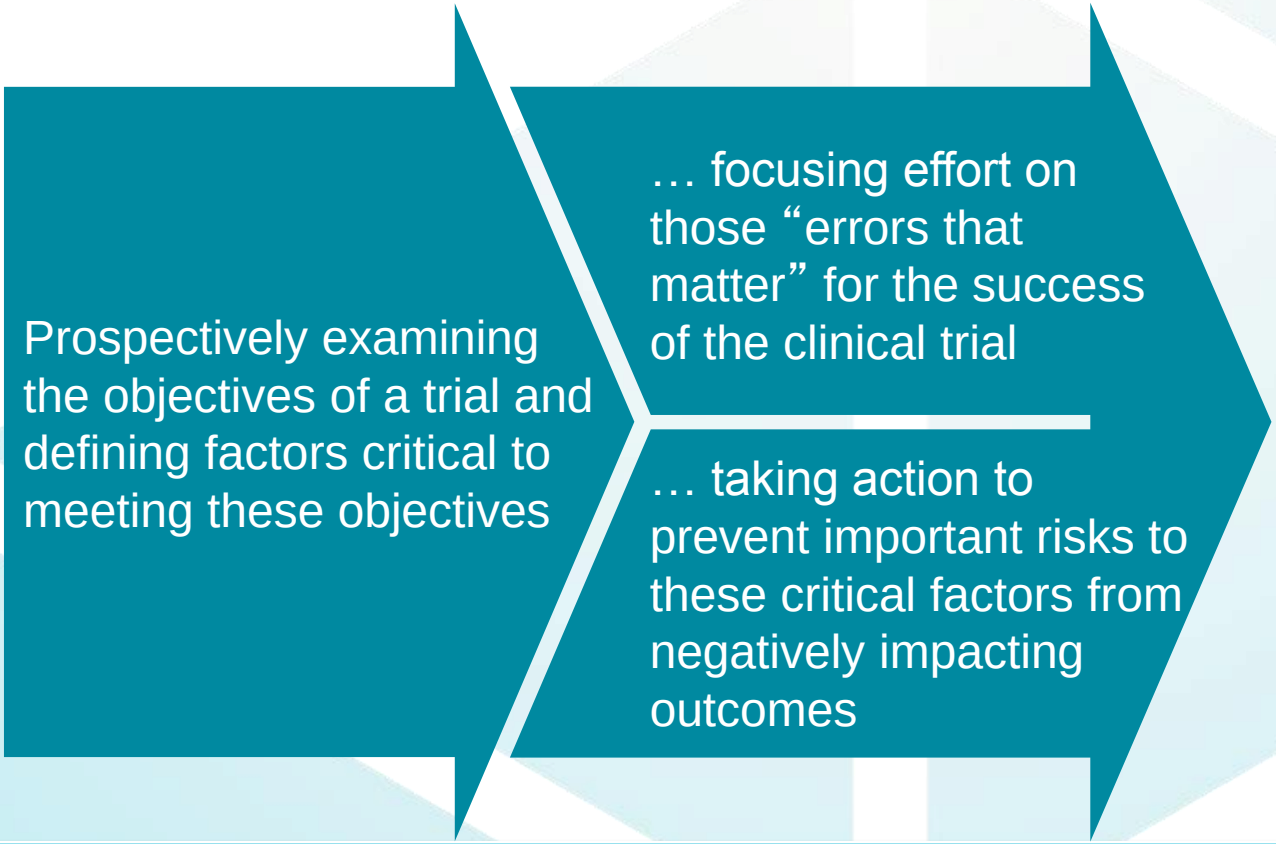
Quality by Design: QbD Defined

"Quality" in clinical trials is defined as the absence of errors that matter to decision-making



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**

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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

http://www.ctti-clinicaltrials.org/what-we-do/investigational-plan/qbd-qrm/products

Implementation: Our Response

Need:

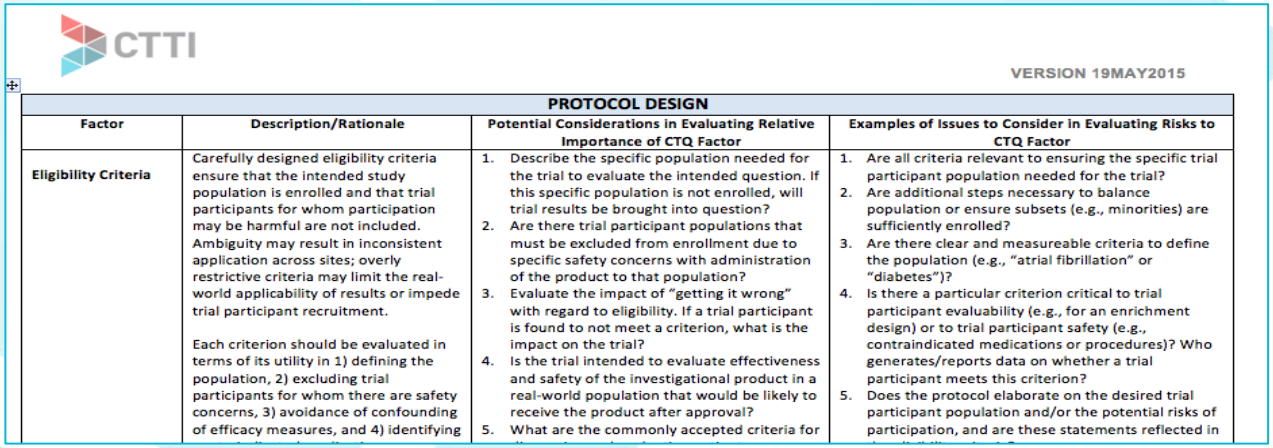
- Participants wanted the QbD Principles to be finalized and published

Supporting materials:

- Publication developed including

  1) CTTI Recommendations,

  2) Appendix with updated Principles Document



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VERSION 19MAY2015

PROTOCOL DESIGN			
Factor	**Description/Rationale**	**Potential Considerations in Evaluating Relative Importance of CTQ Factor**	**Examples of Issues to Consider in Evaluating Risks to CTQ Factor**
Eligibility Criteria	Carefully designed eligibility criteria ensure that the intended study population is enrolled and that trial participants for whom participation may be harmful are not included. Ambiguity may result in inconsistent application across sites; overly restrictive criteria may limit the real-world applicability of results or impede trial participant recruitment. Each criterion should be evaluated in terms of its utility in 1) defining the population, 2) excluding trial participants for whom there are safety concerns, 3) avoidance of confounding of efficacy measures, and 4) identifying	1. Describe the specific population needed for the trial to evaluate the intended question. If this specific population is not enrolled, will trial results be brought into question? 2. Are there trial participant populations that must be excluded from enrollment due to specific safety concerns with administration of the product to that population? 3. Evaluate the impact of "getting it wrong" with regard to eligibility. If a trial participant is found to not meet a criterion, what is the impact on the trial? 4. Is the trial intended to evaluate effectiveness and safety of the investigational product in a real-world population that would be likely to receive the product after approval? 5. What are the commonly accepted criteria for	1. Are all criteria relevant to ensuring the specific trial participant population needed for the trial? 2. Are additional steps necessary to balance population or ensure subsets (e.g., minorities) are sufficiently enrolled? 3. Are there clear and measureable criteria to define the population (e.g., "atrial fibrillation" or "diabetes")? 4. Is there a particular criterion critical to trial participant evaluability (e.g., for an enrichment design) or to trial participant safety (e.g., contraindicated medications or procedures)? Who generates/reports data on whether a trial participant meets this criterion? 5. Does the protocol elaborate on the desired trial participant population and/or the potential risks of participation, and are these statements reflected in

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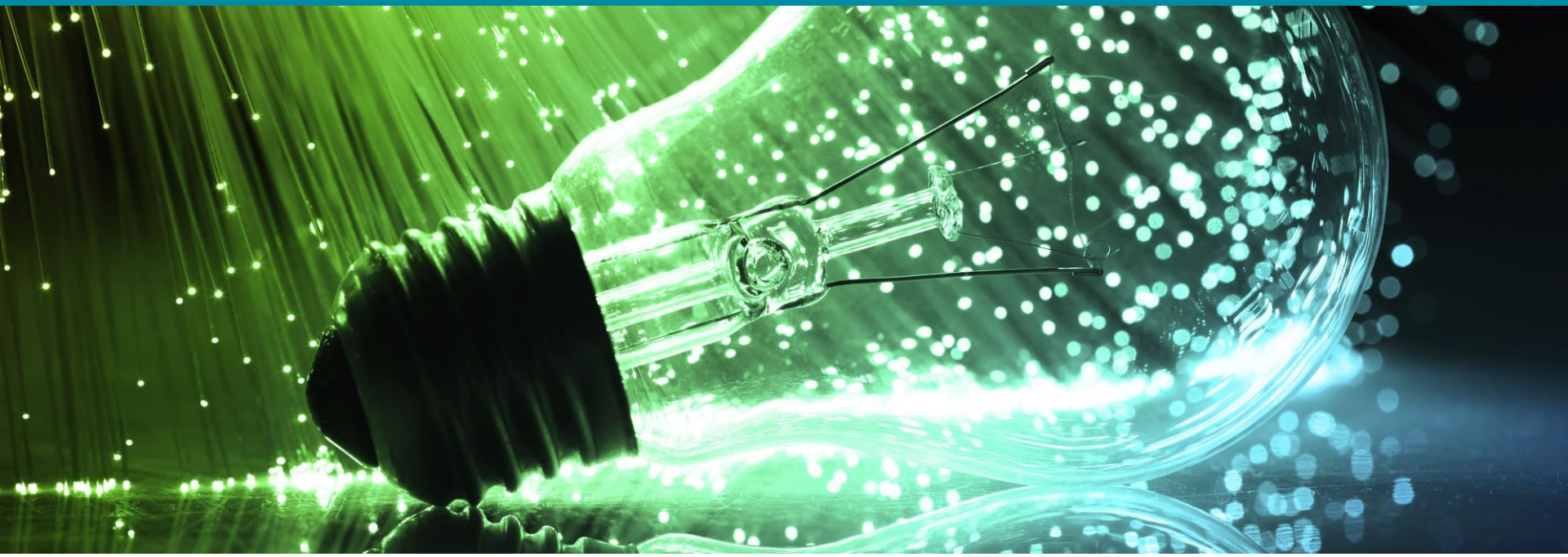


Quality by Design Project Recommendations

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

- 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

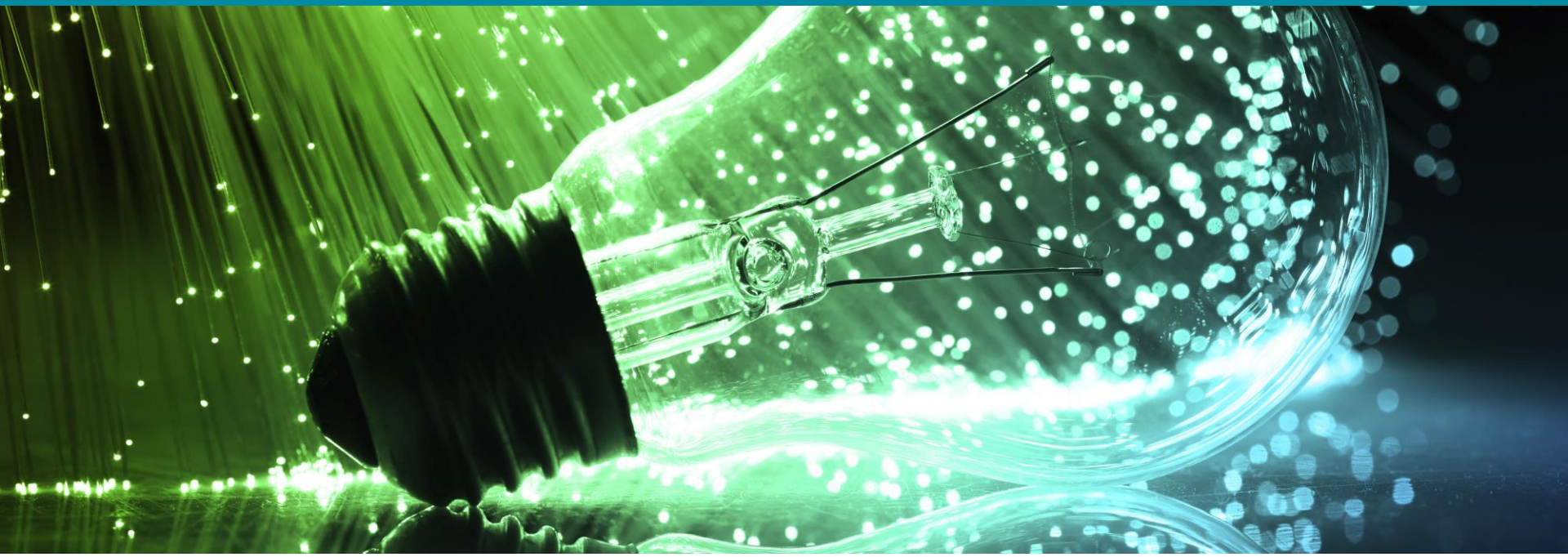
- Rigorously evaluate study design to verify that planned activities and data collection are essential.
- Streamline trial design wherever feasible.
- Deploy resources to identify and prevent or control errors that matter in the study.
- Consider whether nonessential activities may be eliminated from 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

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Toolkit: Learn About Quality by Design

Learn About QbD

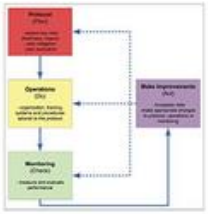
This section of the Toolkit provides an introduction to QbD through videos, downloadable presentations, and peer-reviewed articles. Learn about QbD and why it matters in clinical trials. Leverage these tools to teach others in your organization about QbD in order to secure their interest and support.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



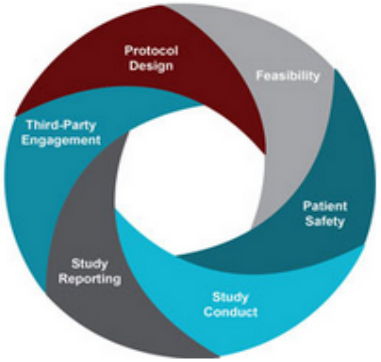
QbD Publication in DIJ

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

Toolkit: Teach Others About Quality by Design

Teach Others About QbD



QbD is about prospectively examining the objectives of a clicinal 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

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Toolkit: Workshop Tools

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

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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

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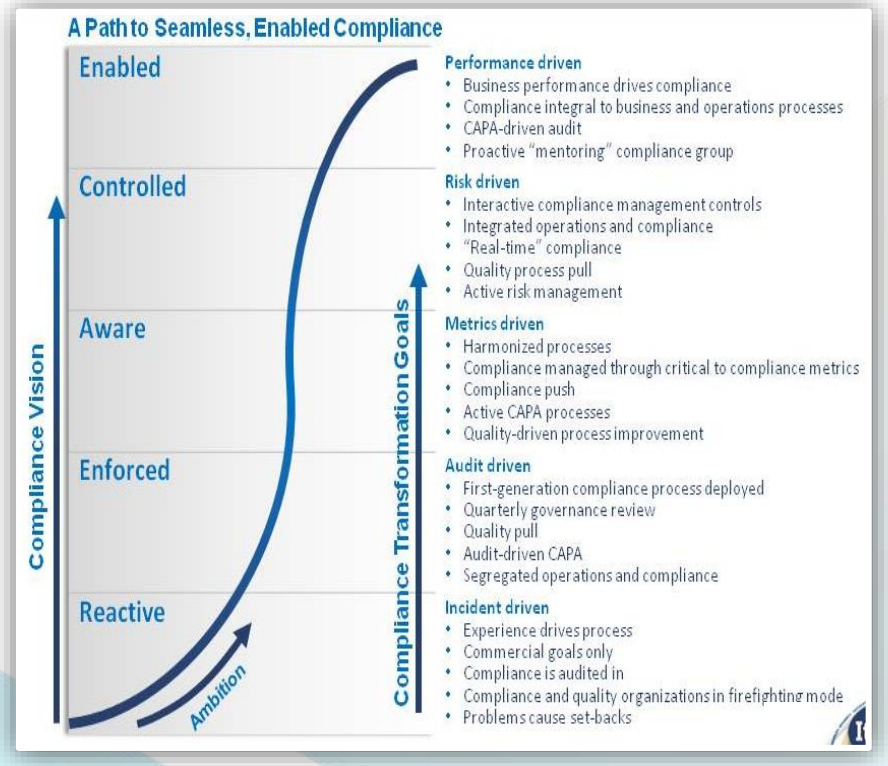
Sustaining Clinical Quality-by-Design Requires A Quality Culture



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

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)

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Additional Information & Resources

- View the Toolkit at http://www.ctti-clinicaltrials.org/toolkit/QbD
- Access the Principles Document directly at http://www.ctti-clinicaltrials.org/what-we-do/investigational-plan/qbd-qrm/products
- To view recordings of previous webinars from the CTTI-hosted webinar series, and general CTTI QbD resources visithttp://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
- Find additional CTTI resources on our website, www.ctti-clinicaltrials.org

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Thank you.

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