CLINICAL TRIALS TRANSFORMATION INITIATIVE

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Efficiency and Quality by Design

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Disclaimer

- The views and opinions expressed in this presentation are those of the individual presenter and do not necessarily reflect the views of the Clinical Trials Transformation Initiative.
- Pamela Tenaerts is an Employee of Duke University. Salary support comes from pooled membership fees of the Clinical Trials Transformation Initiative and from FDA grant R18FD005292.

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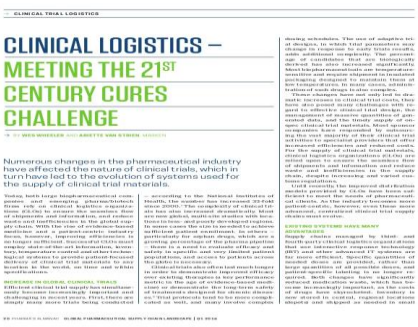
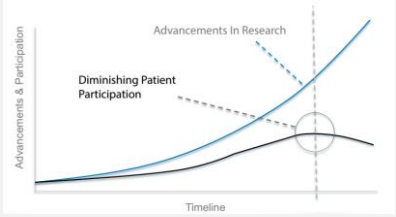
Clinical Trials are in Crisis



CLINICAL TRIAL LOGISTICS

CLINICAL LOGISTICS – MEETING THE 21ST CENTURY CURES CHALLENGE

Numerous changes in the pharmaceutical industry have affected the nature of clinical trials, which in turn have led to the evolution of systems used for the supply of clinical trial materials.



Forbes

Discovery's 'First In Human' Calls Much-Needed Attention To Clinical Trials

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Addressing this need

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

Public-Private Partnership
Co-founded by Duke University & FDA

Involves all stakeholders
- Approx. 80 member orgs
- Participation of 400+ more orgs

Mission: To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials

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CTTI Activities

Quality	Patient Engagement	Investigators & Sites
Quality by Design	Patient Groups & Clinical Trials	Investigator Community
Diversity	Patient Engagement Collaborative	Investigator Qualification
Informing ICH E6 Renovation		GCP Training
Analysis of ClinicalTrials.gov		Site Metrics
Recruitment		
Planning for Pregnancy Testing		
State of Clinical Trials Report		
Monitoring		

Mobile Clinical Trials	Novel Clinical Trial Designs	Ethics & Human Research Protection
Novel Endpoints	Real World Data for Eligibility and Recruitment	Single IRB
Mobile Technologies	Master Protocols (VeloCTTI)	Data Monitoring Committees
Decentralized Clinical Trials	Registry Trials	Informed Consent
Engaging Patients and Sites	Antibacterial Drug Development (early consent)	Safety Reporting
Feasibility Studies Database	Sentinel IMPACT-Afib Trial	
	Large Simple Trials	
	Using FDA Sentinel for Trials	

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Examples of Impact

- Organization level adoption
  - CTTI's Single IRB tools & recommendations are used by organizations such as the National Institute of Neurological Disorders and Stroke (NIH) and North Shore-LIJ Health System
  - CTTI's Quality by Design framework is used by organizations such as AstraZeneca, DCRI, The Medicines Company, PCORNET, Pfizer, Target Health Inc. and University of Oxford
  - The Cystic Fibrosis Foundation has applied CTTI's recommendations to improve its DMC operations
  - Eli Lilly is implementing CTTI's informed consent recommendations through their e-consent model
- Policy Adoption: EMA reflection paper, FDA guidance documents, ICH renovation paper, and NIH draft policy

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Quality by Design (QbD)

The need for QbD

- Current approach to trial monitoring not effective (2008)
- 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

DiMasi JA. *Cost of developing a new drug*, http:// csdd.tufts.edu/files/uploads/Tufts_CSDD_briefing_on_ RD_cost_study_ Nov_18,_2014.pdf.

Getz KA, Stergiopoulos S, Marlborough M, et al. Quan- tifying the magnitude and cost of collecting extraneous protocol data. *Am J Ther* 2015; 22: 117–124.

http://csdd.tufts.edu/files/uploads/Summary-JanFebIR2016_.pdf

http://dij.sagepub.com/content/46/6/657

Streamlining Trial Design

"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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Impact of Protocol Complexity on Trial Performance

(All TAs, Phases II-III)

	Less Complex	More Complex	Difference
Study volunteer screen to completion rate	56%	23%	Halved
Time from Protocol Ready to FPFV (median)	115 days	129 days	+12%
Time from Protocol Ready to LPLV (median)	413 days	714 days	+73%
Number of Amendments	1.9	3.2	+68%

Getz et al. Assessing the Impact of Protocol Design Change on Clinical Trial Performance. AJT 2008 15(5); 450 - 457

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Building Quality into the Scientific and Operational Design of Trials

- Prospectively identify the aspects of a trial that are "critical to quality"
- Identify important and likely risks to "critical to quality" aspects
- Tailor the investigational plan and trial implementation to eliminate or reduce the impact of "errors that matter"

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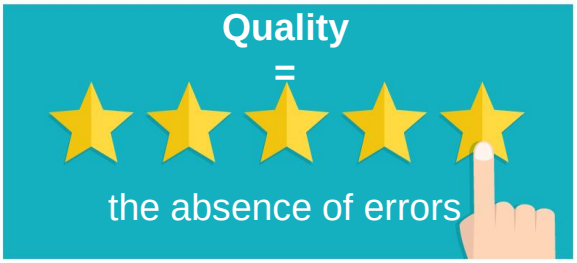
CTTI QbD Recommendations



That matter to decision making

That have a meaningful impact

- on the safety of trial participants
- on credibility of the results

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CTTI QbD Recommendations

- Create a culture that:
  - Values and rewards critical thinking and open dialogue about quality
  - Goes beyond sole reliance on tools and checklists
- Focus effort on activities that are essential to the credibility of the study outcomes
- Involve a broad range of stakeholders in protocol development and discussions around study quality
- Prospectively identify and periodically review the critical to quality factors

Enhancing clinical evidence by proactively building quality into clinical trials
https://journals.sagepub.com/doi/full/10.1177/1740774516643491

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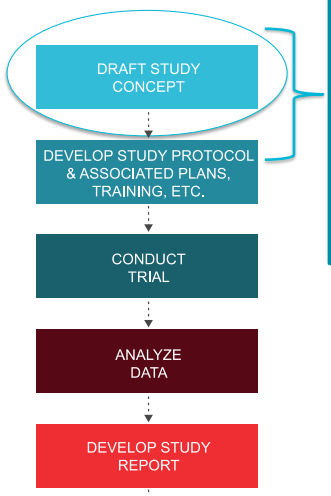
Study design: (concept to final protocol)



1. Identify critical to quality (CTQ) aspects of trial design and potential challenges in these areas
2. Tailor design to avoid errors that could undermine evaluability or safety
3. Streamline trial where feasible (patient, operational, and scientific impact)
4. Verify proposed design consistent with important scientific question to be addressed and leverages appropriate, accepted measures
5. Highlight and evaluate important risks in critical to quality areas that cannot be eliminated through study design

Translate into efficient, focused trial implementation and oversight.

1. Identify and implement targeted strategies to reduce key risks in CTQ areas
2. Tailor operational oversight plans (e.g. monitoring, data management) to focus on early detection of important errors not eliminated through trial design ("Focus effort on activities that are essential to the credibility of the study outcomes")

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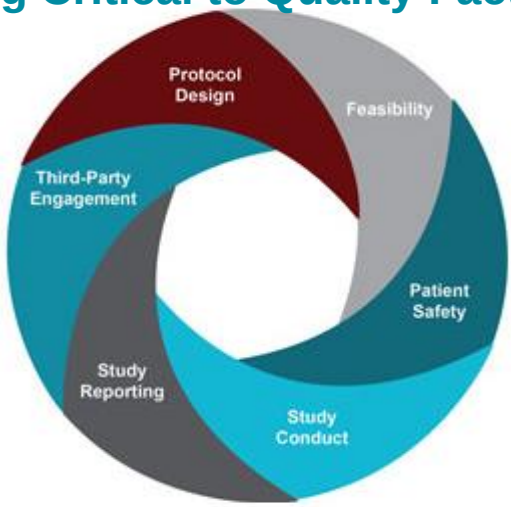
Principles Document: Exploring Critical to Quality Factors



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

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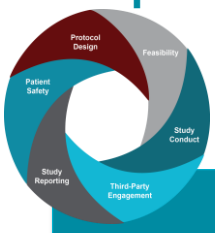
QbD Implementation Tool: Principles Document



The Principles document is a resource that facilitates critical thinking and quality planning. It helps organizations gain a clear understanding of events that can …

… impede the conduct of the study

… place subjects at unnecessary risk

… hinder efforts to use resulting data to answer the scientific questions being addressed

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PROTOCOL DESIGN SHOW ALL HIDE ALL TOP

Eligibility Criteria	SHOW DETAILS
Randomization	SHOW DETAILS
Masking	SHOW DETAILS
Types of Controls	SHOW DETAILS
Data Quantity	SHOW DETAILS
Endpoints	SHOW DETAILS
Procedures Supporting Study Endpoints and Data Integrity	SHOW DETAILS
Investigational Product (IP) Handling and Administration	SHOW DETAILS

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PROTOCOL DESIGN SHOW ALL HIDE ALL TOP

Endpoints HIDE DETAILS

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?

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ICH guidelines & QbD

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ICH E guidelines:

E8 General Considerations for Clinical Trials

Design and analysis:
E4 Dose-Response Studies
E9 Statistical Principles for Clinical Trials
E10 Choice of Control Group in Clinical Trials
E17 Multi-Regional Clinical Trials

Conduct and reporting:
E3 Clinical Study Reports
E6 Good Clinical Practice

Safety reporting:
E1 Clinical Safety for Drugs used in Long-Term Treatment
E2A - E2F Pharmacovigilance
E14 Clinical Evaluation of QT
E19 Safety Data Collection

Populations:
E5 Ethnic Factors
E7 Clinical Trials in Geriatric Population
E11 - E11A Clinical Trials in Pediatric Population
E12 Clinical Evaluation by Therapeutic Category

Genetics/genomics:
E15 Definitions in Pharmacogenetics / Pharmacogenomics
E16 Qualification of Genomic Biomarkers
E18 Genomic Sampling

https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/ICHE8_R1__Step_2_Presentation_2019_0606.pdf

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ICH E guidelines

- The ICH Efficacy guidelines cover the design, conduct, analysis and reporting of clinical studies. The guidelines should be used in an integrated manner rather than one or other guideline or subsection being focused on in isolation of the others.
- E8(R1) provides an overall introduction to clinical development, designing quality into clinical studies and focusing on those factors critical to the quality of the studies
  - Quality by design
  - Development Planning
  - Design Elements for Clinical Studies

https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/ICHE8_R1__Step_2_Presentation_2019_0606.pdf

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ICH E8 R(1) Key principles

- Protection of clinical study participants is a shared responsibility (investigators, sponsors, IRB/IECs).
- Clinical studies should be designed, conducted, and analyzed according to sound scientific principles and reported appropriately.
- Consulting with patients and/or patient organizations in the design, planning and conduct of clinical studies helps to ensure that all perspectives are captured.

https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/ICHE8_R1__Step_2_Presentation_2019_0606.pdf

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ICH E8 (R) QbD Concepts

- Quality of a clinical study is fitness for purpose. The quality of the information generated should therefore be sufficient to support good decision making.
- The quality of a study is driven proactively by designing quality into the study protocol and processes.
- Critical to quality factors should be determined for each study
- Risks that threaten the integrity of the critical to quality factors should be identified and managed in a proportionate manner

https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/ICHE8_R1__Step_2_Presentation_2019_0606.pdf

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Online Resources

- CTTI website → What We Do → QbD
  - Project overview
  - Recommendations
  - Webinars
  - Publications
  - Presentations
  - Principles Document
- QbD Toolkit

https://www.ctti-clinicaltrials.org/projects/quality-design

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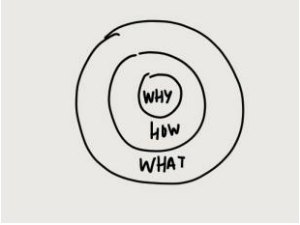
QbD Adoption Project - Objectives



- Demonstrate ways in which QbD addresses challenges and needs of clinical trials stakeholders
- Provide examples of implementing QbD in clinical trials in ways that can be emulated and adapted by the broad range of stakeholders
- Drive adoption of QbD across the clinical trials enterprise

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Planned New Resources

- Detailed case studies on implementation of QbD (retrospective and prospective)
- Framework for selecting appropriate process and outcome metrics
- QbD maturity model
- Updated QbD toolkit
- Presentations and articles as appropriate to enhance awareness and understanding of QbD

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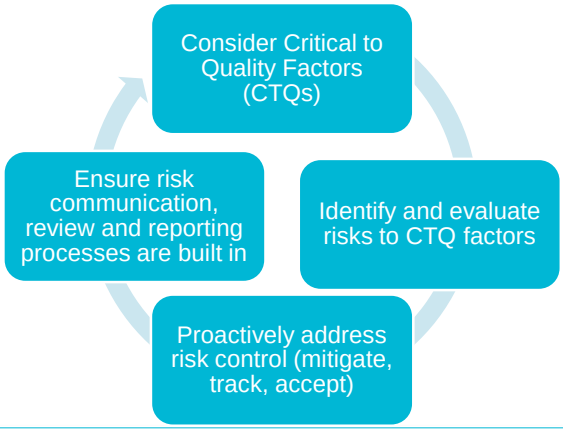
Quality by Design

Strengthens the foundation of clinical studies by promoting quality management and risk-based approaches throughout study design and conduct:



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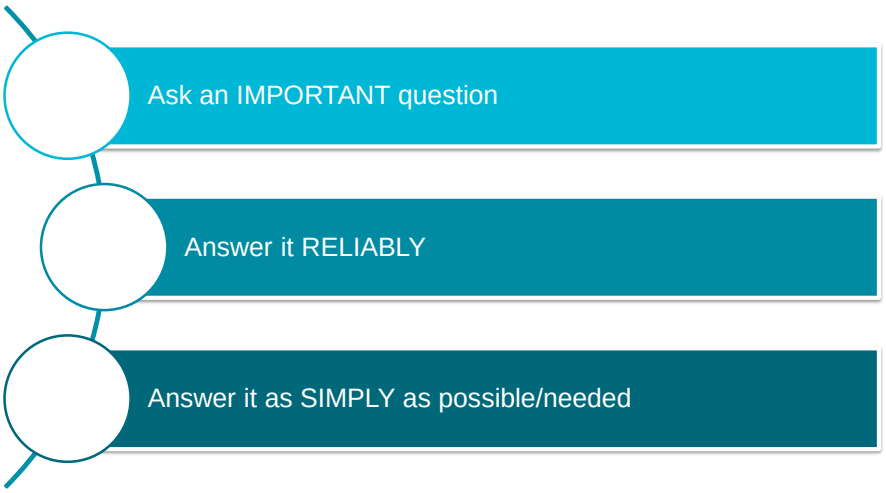
Criteria of a good trial



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THANK YOU.

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www.ctti-clinicaltrials.org