

Welcome to: Accelerating Evidence Generation – Resources for Implementing a QbD Approach to Clinical Trials

- This webinar is being recorded and will be posted to the CTTI website
- All participants are muted upon entry
- Questions can be entered in the chat box during the webinar
- There will be a “Question & Answer” session at the end of the webinar



CLINICAL
TRIALS
TRANSFORMATION
INITIATIVE

November 12, 2020

Accelerating Evidence Generation – Resources for Implementing a QbD Approach to Clinical Trials

Ansalan Stewart, FDA

David Rodin, Amici Clinical Research

Greg Pennock, EMD Serono

Karlin Schroeder, Parkinson's Foundation

Steve Young, CluePoints

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 or of the organizations with which the presenters are individually associated.



Multi-stakeholder,
public-private partnership
co-founded by Duke University & FDA

Participation of 500+ more orgs and
± 80 member organizations

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



Re-Framing Quality

“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)

Example: Cardiovascular Major Morbidity Outcomes Trial

- Critical-to-quality: strategies to ensure the survival status of all trial participants is captured
- Not critical-to-quality: source verifying participants’ temperature readings obtained as a part of vital sign assessments at routine study visits

QbD Adoption Project Team (2018-Present)

Executive Committee Champions

- ▶ John Alexander (Duke)
- ▶ Donna Cryer (Global Liver Institute)

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- ▶ Louise Bowman (U. of Oxford)
- ▶ Dagmar Görtz (Janssen)
- ▶ Karlin Schroeder (Parkinson's Foundation)
- ▶ Ansalan Stewart (FDA/CDER)

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- ▶ Craig Reist (Duke)*
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- ▶ Margaret Schneider (UC Irvine)
- ▶ Fergus Sweeney (EMA)
- ▶ Mary Taylor (BD)

*Former team member | **Former team leader

Brief Agenda

Time (ET)	Topic	Presenter
12:05 p.m.	Quality by Design: Why it Matters	Ansalan Stewart & Karlin Schroeder
12:15 p.m.	Case Study: Getting Started with QbD	Greg Pennock
12:25 p.m.	Scaling Up: QbD Maturity Model	David Rodin
12:35 p.m.	Quantifying Outcomes: QbD Metrics Framework	Steve Young
12:45 p.m.	Closing Comments and Q&A	

All resources discussed today are freely available at <https://www.ctti-clinicaltrials.org/projects/quality-design>

Quality by Design: Why it Matters

Ansalan Stewart,
FDA



Karlin Schroeder,
Parkinson's
Foundation



Managing Trial Risks

1. Collaboratively identify critical aspects of trial during protocol design

2. Evaluate risks in these critical areas

3. Determine whether each risk is best mitigated through:
a) trial design,
b) implementation of risk-based trial oversight, or
c) a combination of design and oversight

Trial Design

Action: Optimize critical elements of trial design to eliminate and/or reduce the risk of important errors

Outcome: Operationally feasible trial design

Trial Oversight

Action: Design monitoring and other oversight plans focused on mitigating risks not addressed through trial design and/or that may arise from trial implementation

Outcome: Risk-informed trial quality management

CTTI Quality by Design Recommendations



Create a **culture** that:

- Values and rewards critical thinking and open dialogue about quality
- Goes beyond sole reliance on tools and checklists



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



Prospectively identify and periodically review the **critical to quality factors**



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

Ongoing “GCP Renovation” May Incorporate QbD Concepts into ICH E8

TABLE OF CONTENTS

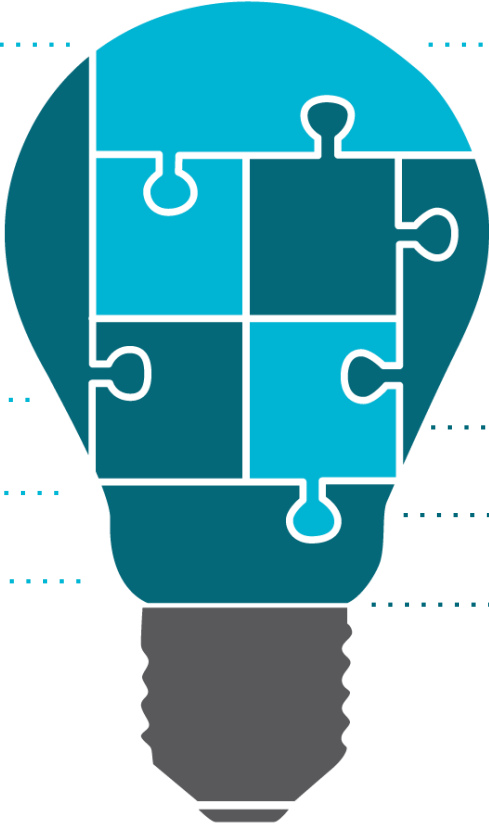
1	OBJECTIVES OF THIS DOCUMENT	1
2	GENERAL PRINCIPLES	2
2.1	Protection of Clinical Study Subjects.....	2
2.2	Scientific Approach in Clinical Study Design, Conduct, and Analysis	2
2.3	Patient Input into Study Design	3
3	DESIGNING QUALITY INTO CLINICAL STUDIES	4
3.1	Quality by Design of Clinical Studies.....	4
3.2	Critical to Quality Factors	5
3.3	Approach to Identifying the Critical to Quality Factors	6
3.3.1	Establishing a Culture that Supports Open Dialogue	6
3.3.2	Focusing on Activities Essential to the Study.....	7
3.3.3	Engaging Stakeholders in Study Design.....	7
3.3.4	Reviewing Critical to Quality Factors	8

ICH E8(R1) Draft 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.

Engaging the Broad Range of Stakeholders

Perspectives to include in Quality by Design discussions may include these and others:

- 
- Senior Advocate
 - Clinical / Medical
 - Biostatistics
 - Medical Writing
 - Clinical Operations
 - Clinical Data Management
 - Safety / Pharmacovigilance
 - Regulatory Affairs
 - Clinical Supply Chain
 - Clinical Quality Management & Assurance
 - Investigative Site Staff
 - CRO
 - Patients, Caregivers & Patient Advocacy Groups



INTERNAL PERSPECTIVE



EXTERNAL PERSPECTIVE



New Resource: QbD Implementation Guide for Individual Clinical Trials

- ▶ Helps study teams plan implementation
- ▶ Supports ongoing self-evaluation and continuous improvement
- ▶ Addresses:
 - Awareness & Supports
 - Incentives
 - **Stakeholder Engagement**
 - Critical-to-Quality Focus
 - Handover from Study Design to Execution
 - Management of Risks to Critical-to-Quality Factors
 - Lessons Learned
 - Continuous Improvement Metrics

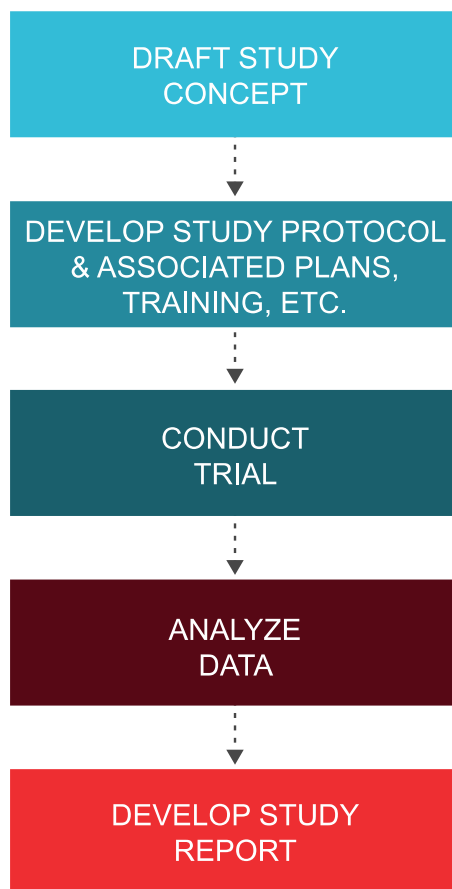
Factor	Component
Stakeholder Engagement	Identify the broad range of internal and external stakeholders to engage in study design (see suggestions here)
	Engage identified internal stakeholders as equal partners from the earliest stages of study design
	Engage identified patient representatives as equal partners from the earliest stages of study design
	Engage identified CRO representatives and other operational partners from the earliest stages of study design (ideally in RFP stage)
	Engage identified investigative site personnel from the earliest stages of study design
	Engage regulators early in study design, if appropriate (e.g., when a study has novel features in elements considered critical to quality)

Case Study: Getting Started with QbD

Greg Pennock, EMD Serono




QbD Approach to Study Design



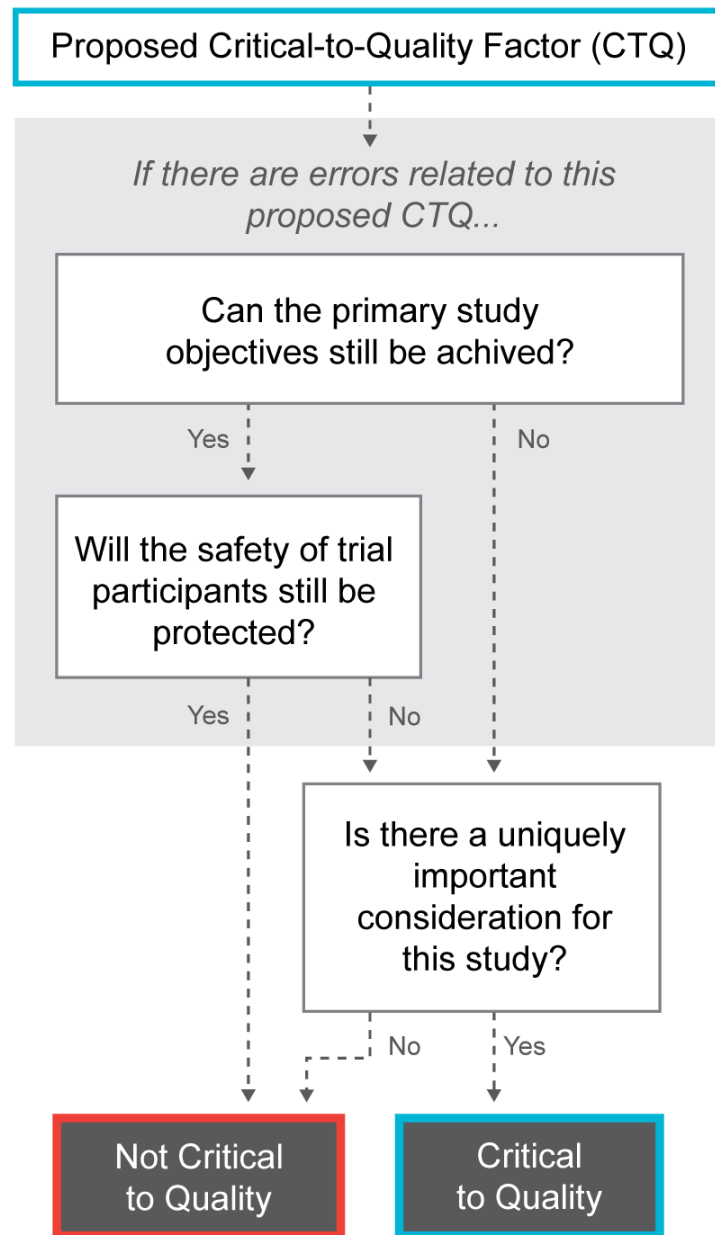
Engage all stakeholders to...

- Identify critical to quality aspects of trial design and potential challenges
- Tailor design to avoid errors that could undermine evaluability or safety
- Streamline trial where feasible
- Verify proposed design consistent with scientific question
- Highlight and evaluate residual risks

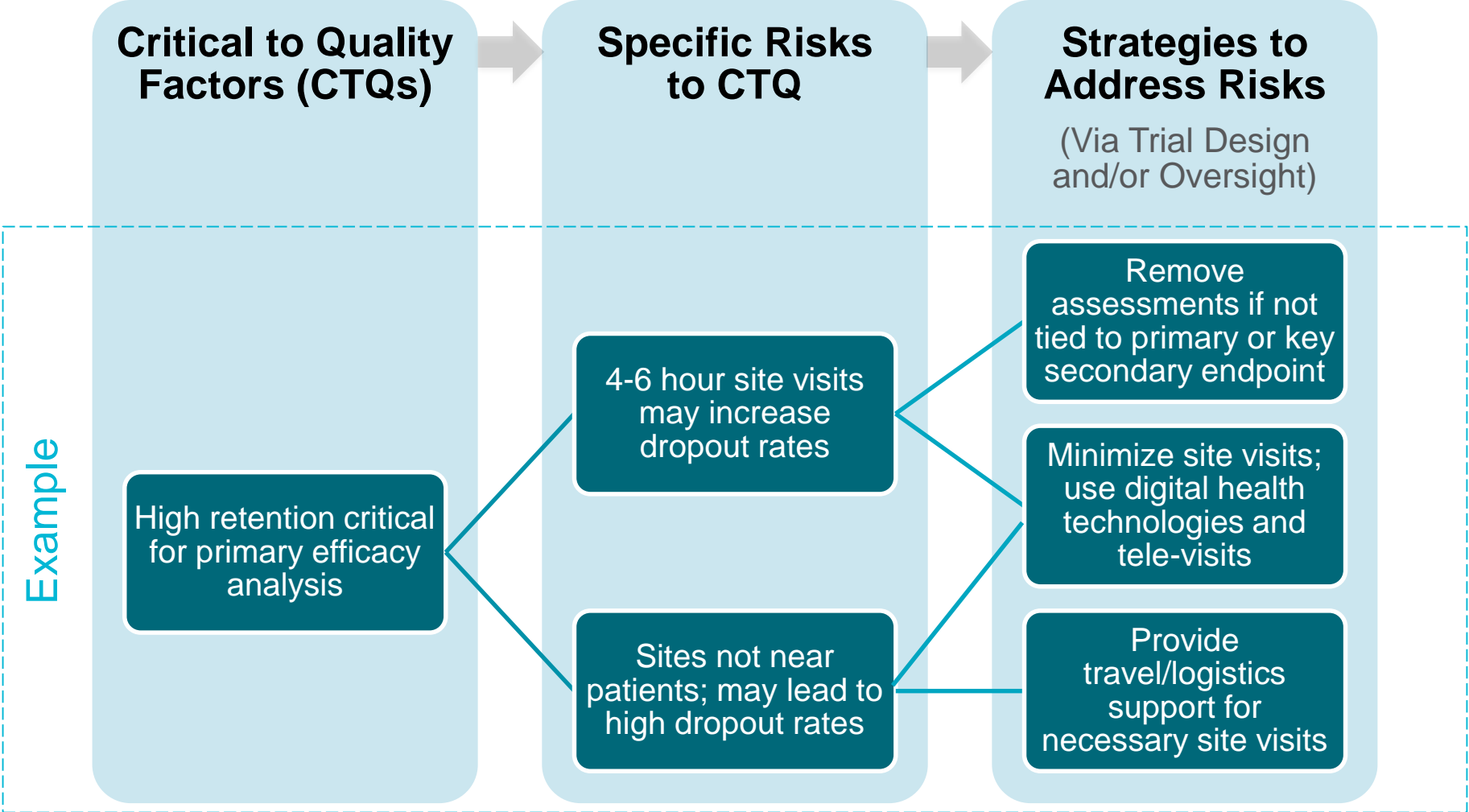
- 
- Operationally feasible trial design
 - Efficient, focused trial oversight plans (e.g., monitoring, data management)

Any Element of the Study Can be “Critical to Quality”

Topic	Examples of Potential CTQ Factors
Protocol Design	Eligibility Criteria Randomization Masking Types of Controls Data Quantity Endpoints Procedures Supporting Study Endpoints and Data Integrity IP Handling and Administration
Feasibility	Study and Site Feasibility Accrual
Patient Safety	Informed Consent Withdrawal Criteria and Trial Participant Retention Signal Detection and Safety Reporting Data Monitoring Committee /Stopping Rules
Study Conduct	Training Data Recording and Reporting Data Monitoring and Management Statistical Analysis
Study Reporting	Dissemination of Study Results
Third-Party Engagement	Delegation of Sponsor Responsibilities Collaborations



Operationalizing the Critical to Quality Factors



Scaling Up: QbD Maturity Model

David Rodin, Amici Clinical Research



Maturity Models

What are they?

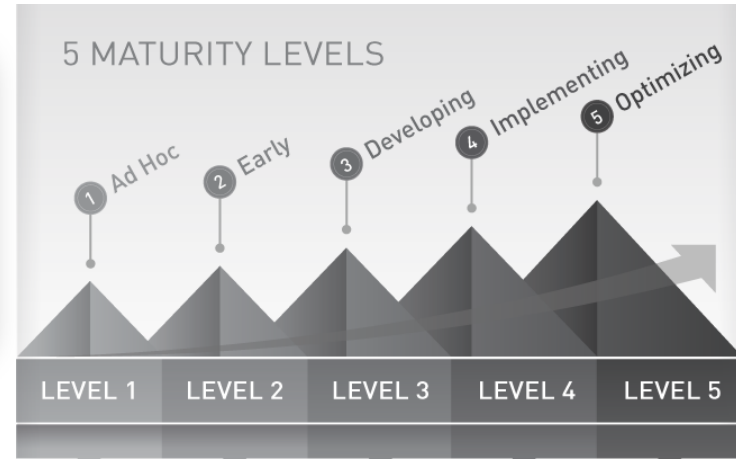
- A subjective, yet structured way to evaluate progress
- A holistic view of the major areas that are important for progress
- A breakdown of major areas into key elements that tend to be more practical and definable
- A set of levels that, while based on an overarching concept of attainment, are specifically defined for each key element.

Why use them?

- Provide a broad approach to the topic necessary for success
- Give practical ways to
 - Measure in the absence of hard metrics
 - Establish goals
 - Gain organizational buy-in

New Resource: QbD Maturity Model

For today's assessment, what department or organizational level are you addressing?



QUALITY CULTURE

- Awareness & Supports
- Incentives

STUDY DESIGN

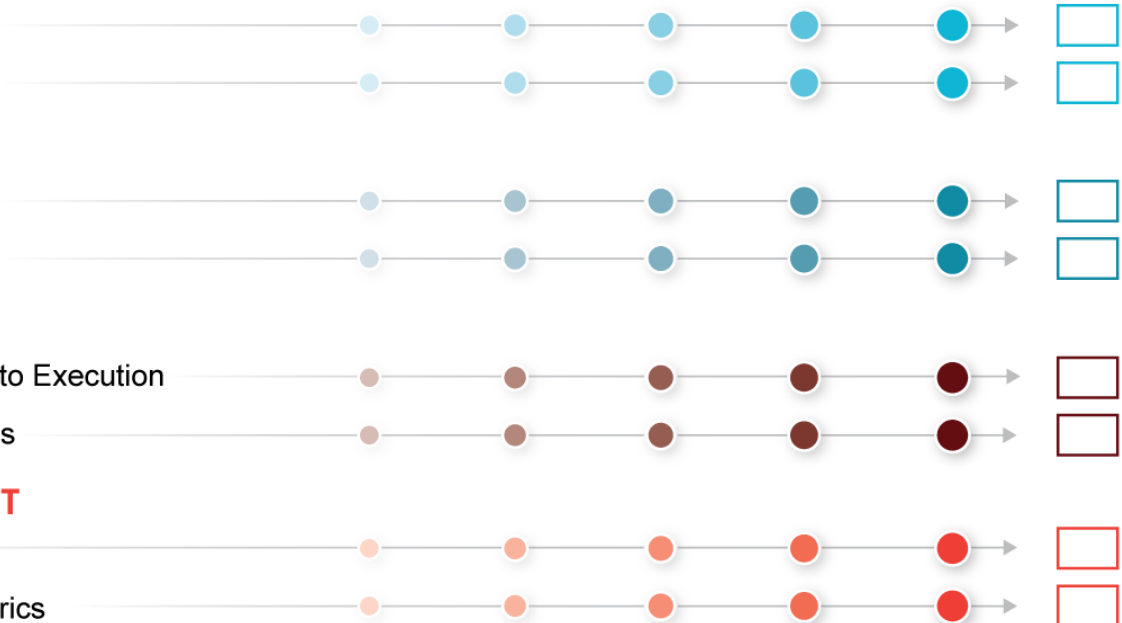
- Stakeholder Engagement
- Critical-to-Quality Focus

STUDY CONDUCT

- Handover from Study Design to Execution
- Management of Risks to CTQs

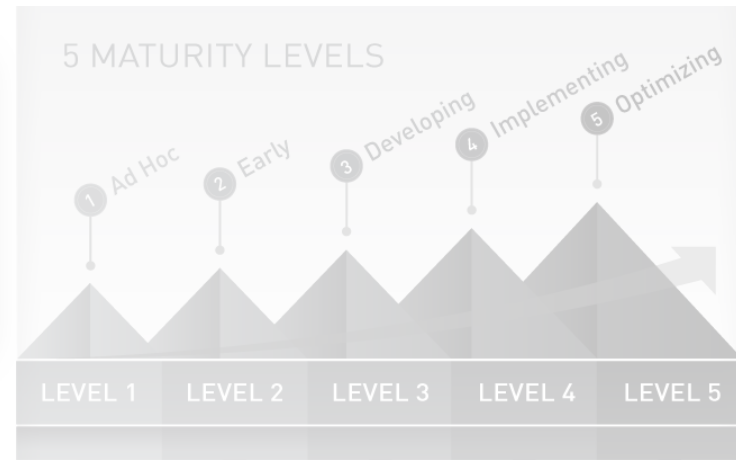
CONTINUOUS IMPROVEMENT

- Lessons Learned
- Continuous Improvement Metrics



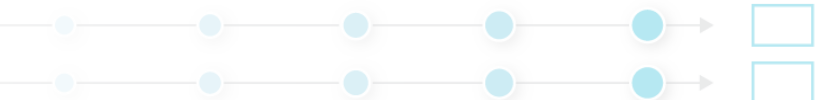
Example: Assessing “Study Design” Factors

For today’s assessment, what department or organizational level are you addressing?



QUALITY CULTURE

- » Awareness & Supports
- » Incentives



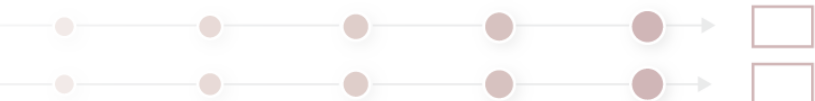
STUDY DESIGN

- » Stakeholder Engagement
- » Critical-to-Quality Focus



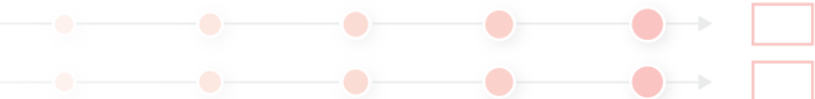
STUDY CONDUCT

- » Handover from Study Design to Execution
- » Management of Risks to CTQs



CONTINUOUS IMPROVEMENT

- » Lessons Learned
- » Continuous Improvement Metrics



Level Descriptions (example cont'd)

Factors:	Level 1 Ad hoc	Level 2 Early	Level 3 Developing	Level 4 Implementing	Level 5 Optimizing
Stakeholder Engagement	Study designed with input primarily from protocol writing team	Study design considers some, but not all, stakeholders' needs	Study design identifies and considers all stakeholders' needs; not all stakeholders directly engaged	Study design includes direct engagement with all stakeholders from earliest stages of study planning	Study design collaboratively considers needs of all stakeholders Periodically updating understanding of who the stakeholders are, across the research enterprise, and their current needs
Critical-to-Quality Focus	<p>Protocols include data collection not necessary for patient safety or credibility of findings</p> <p>Critical-to-quality factors (CTQs) not formally identified</p> <p>Operational implications of protocol not fully considered</p>	<p>Data collection considered against study objectives, but non-essential endpoints and assessments remain</p> <p>CTQs and associated risks to study quality discussed, but not systematically addressed</p> <p>Operational implications often not considered until protocol is near-final</p>	<p>All endpoints and assessments considered against scientific rationale, but other factors may still drive decisions</p> <p>Formal process in place for identifying and addressing CTQs</p> <p>Operational implications considered from early stages of protocol design</p>	<p>Study design process enforces strong justification for any study endpoints and assessments beyond the most fundamental</p> <p>CTQs systematically identified and addressed in protocol design, operational planning, and risk management and monitoring</p>	<p>Study design is as simple as possible, with complexity proportionate to objectives</p> <p>Protocol and supporting documents simplified and streamlined, and all protocol-specific training aligned with CTQs</p> <p>Study-specific risks proactively identified, updated and controlled throughout study lifecycle</p>

Current State for “Stakeholder Engagement” (example cont’d)

Factors:	Level 1 Ad hoc	Level 2 Early	Level 3 Developing	Level 4 Implementing	Level 5 Optimizing
Stakeholder Engagement	Study designed with input primarily from protocol writing team	Study design considers some, but not all, stakeholders’ needs	Study design identifies and considers all stakeholders’ needs; not all stakeholders directly engaged	Study includes engagement of stakeholders early in study	Study design includes engagement of stakeholders throughout study lifecycle
Critical-to-Quality Focus	<p>Protocols include data collection not necessary for patient safety or credibility of findings</p> <p>Critical-to-quality factors (CTQs) not formally identified</p> <p>Operational implications of protocol not fully considered</p>	<p>Data collection considered against study objectives, but non-essential endpoints and assessments remain</p> <p>CTQs and associated risks to study quality discussed, but not systematically addressed</p> <p>Operational implications often not considered until protocol is near-final</p>	<p>All endpoints and assessments considered against scientific rationale, but other factors may still drive decisions</p> <p>Formal process in place for identifying and addressing CTQs</p> <p>Operational implications considered from early stages of protocol design</p>	<p>Study design process enforces strong justification for any study endpoints and assessments beyond the most fundamental</p> <p>CTQs systematically identified and addressed in protocol design, operational planning, and risk management and monitoring</p>	<p>Study design is as simple as possible, with complexity proportionate to objectives</p> <p>Protocol and supporting documents simplified and streamlined, and all protocol-specific training aligned with CTQs</p> <p>Study-specific risks proactively identified, updated and controlled throughout study lifecycle</p>

Patients consulted via advisory boards, but not until protocol is nearing completion



Current State for “Critical-to-Quality Focus” (example cont’d)

Factors:	Level 1 Ad hoc	Level 2 Early	Level 3 Developing	Level 4 Implementing	Level 5 Optimizing
Stakeholder Engagement	Study designed with input primarily from protocol writing team	Study design considers some, but not all, stakeholders’ needs	Study design identifies and considers all stakeholders’ needs; not all stakeholders directly engaged	Study design includes direct engagement with all stakeholders from earliest stages of study planning	Study design collaboratively considers needs of all stakeholders Periodically updating understanding of who the stakeholders are, across the research enterprise, and their current needs
Critical-to-Quality Focus	<p>Protocols include data collection not necessary for patient safety or credibility of findings</p> <p>Critical-to-quality factors (CTQs) not formally identified</p> <p>Operational implications of protocol not fully considered</p>	<p>Data collection considered against study objectives, but non-essential endpoints and assessments remain</p> <p>CTQs and associated risks to study quality discussed, but not systematically addressed</p> <p>Operational implications often not considered until protocol is near-final</p>	<p>All endpoints and assessments considered against scientific but other still drive</p> <p>Formal plan for and address CTQs</p> <p>Operational implications considered from early stages of protocol design</p>	<p>Study design process enforces strong justification for any</p> <p>Planning, and non-management and monitoring</p>	<p>Study design is as simple as possible, with complexity proportionate</p> <p>Supporting simplified and, and all specific training CTQs</p> <p>Specific risks identified, updated and controlled throughout study lifecycle</p>

Approach to study planning has some overlap with QbD concepts, but QbD not formally applied



Identifying Desired Future State (example cont'd)

Current State

Desired State (End of 2021)

Factors:	Level 1 Ad hoc	Level 2 Early	Level 3 Developing	Level 4 Implementing	Level 5 Optimizing
Stakeholder Engagement	Study designed with input primarily from protocol writing team	Study design considers some, but not all, stakeholders' needs	Study design identifies and considers all stakeholders' needs; not all stakeholders directly engaged	Study design includes direct engagement with all stakeholders from earliest stages of study planning	Study design collaboratively considers needs of all stakeholders Periodically updating understanding of who the stakeholders are, across the research enterprise, and their current needs
Critical-to-Quality Focus	<p>Protocols include data collection not necessary for patient safety or credibility of findings</p> <p>Critical-to-quality factors (CTQs) not formally identified</p> <p>Operational implications of protocol not fully considered</p>	<p>Data collection considered against study objectives, but non-essential endpoints and assessments remain</p> <p>CTQs and associated risks to study quality discussed, but not systematically addressed</p> <p>Operational implications often not considered until protocol is near-final</p>	<p>All endpoints and assessments considered against scientific rationale, but other factors may still drive decisions</p> <p>Formal process in place for identifying and addressing CTQs</p> <p>Operational implications considered from early stages of protocol design</p>	<p>Study design process enforces strong justification for any study endpoints and assessments beyond the most fundamental</p> <p>CTQs systematically identified and addressed in protocol design, operational planning, and risk management and monitoring</p>	<p>Study design is as simple as possible, with complexity proportionate to objectives</p> <p>Protocol and supporting documents simplified and streamlined, and all protocol-specific training aligned with CTQs</p> <p>Study-specific risks proactively identified, updated and controlled throughout study lifecycle</p>

Quantifying Outcomes: QbD Metrics Framework

Steve Young, CluePoints



New Resource: QbD Metrics Framework

- ▶ Support business case for implementation/scaling
- ▶ Facilitate improvement over time

Includes:

- ✓ Examples of appropriate metrics, including:
 - Leading / interim / lagging indicators
 - How to calculate
 - Implementation considerations
- ✓ Guidelines for selecting set of metrics to support QbD implementation

EXAMPLE METRICS

- Reduced study complexity
- Increased % of important risks mitigated by modifying study design
- Improved rate of patient enrollment
- Reduced rate of important protocol deviations
- Reduced rate of missed assessments for key endpoints
- Lower rate of early terminations
- Increased patient satisfaction with study participation
- Lower rate of avoidable protocol amendments
- Reduced number of major/critical audit findings

Considerations for Selecting and Tracking Metrics

Step 1: Select Relevant Metrics

- What are your primary objectives?
- Which metrics most informative?
- Which feasible to analyze on ongoing basis?
- All metrics directly tied to anticipated QbD outcomes?

Step 2: Identify Meaningful Comparators

- Relevant historical data
- Concurrent studies for which QbD concepts not explicitly applied
- Earlier studies for which QbD concepts *were* applied (i.e., to examine improvement over time)

Step 3: Evaluate Progress Over Time

Overview: Nine Example Metrics

Example Metric	Formula	Desired Trend	Measurable At*	Related QbD Objective
Study Complexity – Endpoints	(# Endpoints Defined in Protocol)	↓ Decrease	▶ Draft study concept ▶ Draft protocol ▶ Final protocol	Streamlining
Percentage of Important Risks Mitigated by Modifying Study Design	$[(\# \text{ of Important Risks Mitigated by Modifying Study Design}) / (\text{Total } \# \text{ of Important Risks Identified During Study Design})] \times 100\%$	↑ Increase	▶ Draft protocol ▶ Final protocol	Both
Rate of Patient Enrollment	$(\# \text{ Patients Enrolled}) / (\# \text{ Sites}) / (\text{Patient Recruitment Period})$	↑ Increase	▶ Intervals until enrollment complete	Streamlining
Rate of Important Protocol Deviations	$(\# \text{ Important Protocol Deviations}) / (\# \text{ Patient Visits})$	↓ Decrease	▶ Intervals during study conduct	Fewer 'Errors that Matter'
Rate of Missed Assessments for Key Endpoints	$(\# \text{ Missed Assessments}) / (\# \text{ Expected Assessments})$	↓ Decrease	▶ Intervals during study conduct	Fewer 'Errors that Matter'
Rate of Early Terminations	$(\text{Total } \# \text{ Early Terminating Patients}) / (\text{Total } \# \text{ Enrolled Patients})$	↓ Decrease	▶ Intervals during study conduct	Fewer 'Errors that Matter'
Patient Satisfaction with Study Participation	Average (Net Promoter Score)	↑ Increase	▶ Early/mid study conduct ▶ Study closeout	Streamlining
Rate of Avoidable Protocol Amendments	(# Avoidable Substantial Protocol Amendments During "Active" Phase of Study)	↓ Decrease	▶ Study closeout	Both
Number of Major and Critical Audit Findings	(# Critical Audit Findings) + (# Major Audit Findings)	↓ Decrease	▶ Study closeout	Both

Overview: Nine Example Metrics

Example Metric	Formula	Desired Trend	Measurable At*	Related QbD Objective
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Patient Satisfaction with Study Participation	Average (Net Promoter Score)	↑ Increase	<ul style="list-style-type: none"> ▶ Early/mid study conduct ▶ Study closeout 	Streamlining
Rate of Avoidable Protocol Amendments	(# Avoidable Substantial Protocol Amendments During "Active" Phase of Study)	↓ Decrease	▶ Study closeout	Both
Number of Major and Critical Audit Findings	(# Critical Audit Findings) + (# Major Audit Findings)	↓ Decrease	▶ Study closeout	Both

Reduced Rate of Important Protocol Deviations

Measurable at intervals during study conduct

DESCRIPTION

Rate of important protocol deviations per patient visit

FORMULA

Metric = (# of Important PDs) /
(# of Patient Visits)

- # of Important PDs** Total number of protocol deviations (PDs) reported during the study that were considered important
- # of Patient Visits** Total number of patient visits conducted during the study across all sites

Formula Notes

- ▶ The term "important" is chosen to align with the definition of "important protocol deviations" provided in the [ICH E3 Q&A document](#), which supplements guidance provided in ICH E3, section 10.2.
- ▶ "# of Patient Visits" is proposed as a denominator to enable normalization of this metric based on a standard unit of study conduct (patient visits) common to most study designs. The opportunity for PDs to occur is generally proportional to the amount of study activity conducted, and patient visits represent a common "unit of study activity". While not all patient visits represent the same amount of activity, this normalization represents an effective method of assessing this metric at aggregate levels.

Increased Percentage of Important Risks Mitigated by Modifying Study Design

Measurable at draft protocol, final protocol

DESCRIPTION

Percentage of important risks mitigated by modifying study design

FORMULA

Metric = [(# of Important Risks Mitigated by Modifying Study Design) / (Total # of Important Risks Identified During Study Design)] x 100%

of Important Risks Mitigated by Modifying Study Design

The subset of important risks that were addressed, in whole or in part, by modifying the study design.

Total # of Important Risks Identified During Study Design

Total number of risks to critical-to-quality factors that were identified during the design of the study.

Formula Notes

- ▶ An “important risk” is defined as the potential for errors that have a meaningful impact on the safety of trial participants or credibility of the results. An important risk should be directly tied to an identified critical-to-quality factor (CTQ). Identifying important risks and CTQs for a given study requires discussion by the broad range of stakeholders.
- ▶ Note that this metric is not assessing the total number or percentage of risks that were eliminated. Rather, it is intended to assess and demonstrate what portion of risks are being addressed in some manner through updates to the study design – and thereby encourage discussions between study designers and their operational colleagues from the earliest stages of study planning, which can often allow for elimination of important risks entirely, and can reduce the temptation to ‘monitor quality in’ after the protocol is near-final.

New Resource: Quality by Design Documentation Tool

1. Decisions on Critical to Quality factors and important risks
2. Design changes made to mitigate important risks
3. Strategies for mitigating risk during study implementation
4. Periodic review/refresh of CTQ factors and mitigations
5. Continuous improvement plans

Identify a relevant scientific question with a legitimate research need.

DRAFT STUDY CONCEPT

- ▶ Identify critical-to-quality factors (CTQs).
- ▶ For each CTQ, identify risks of 'errors that matter.'
- ▶ For each important risk, identify potential mitigation strategies by reviewing lessons learned from prior studies and brainstorming new approaches.

DRAFT STUDY PROTOCOL

- ▶ Review and confirm CTQs.
- ▶ Update risks and mitigation strategies in light of evolving protocol design.

FINAL PROTOCOL

- ▶ Finalize and summarize CTQs, risks and mitigation strategies (both planned and implemented).
- ▶ Create monitoring and training plans as needed that align with identified CTQs.

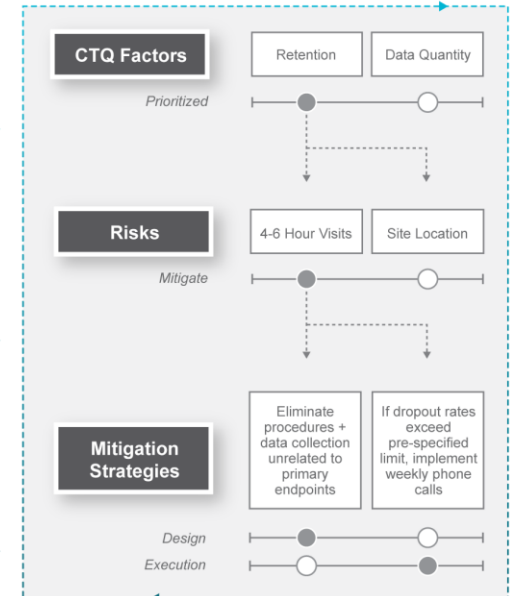
STUDY CONDUCT

- ▶ Regularly manage risks to CTQs.
- ▶ Address issues, systemically if appropriate. Amend protocol if serious design issues arise.

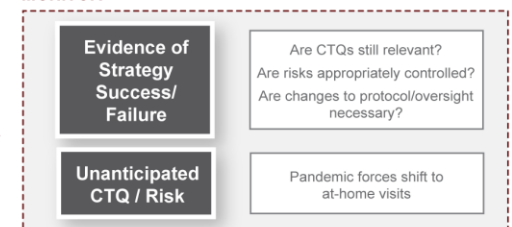
STUDY CLOSEOUT

- ▶ Capture lessons learned. Incorporate into planning of future trials.

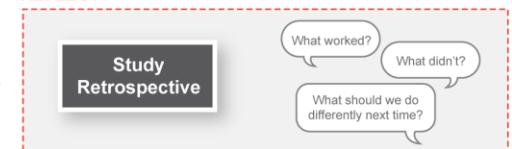
PLAN



MONITOR



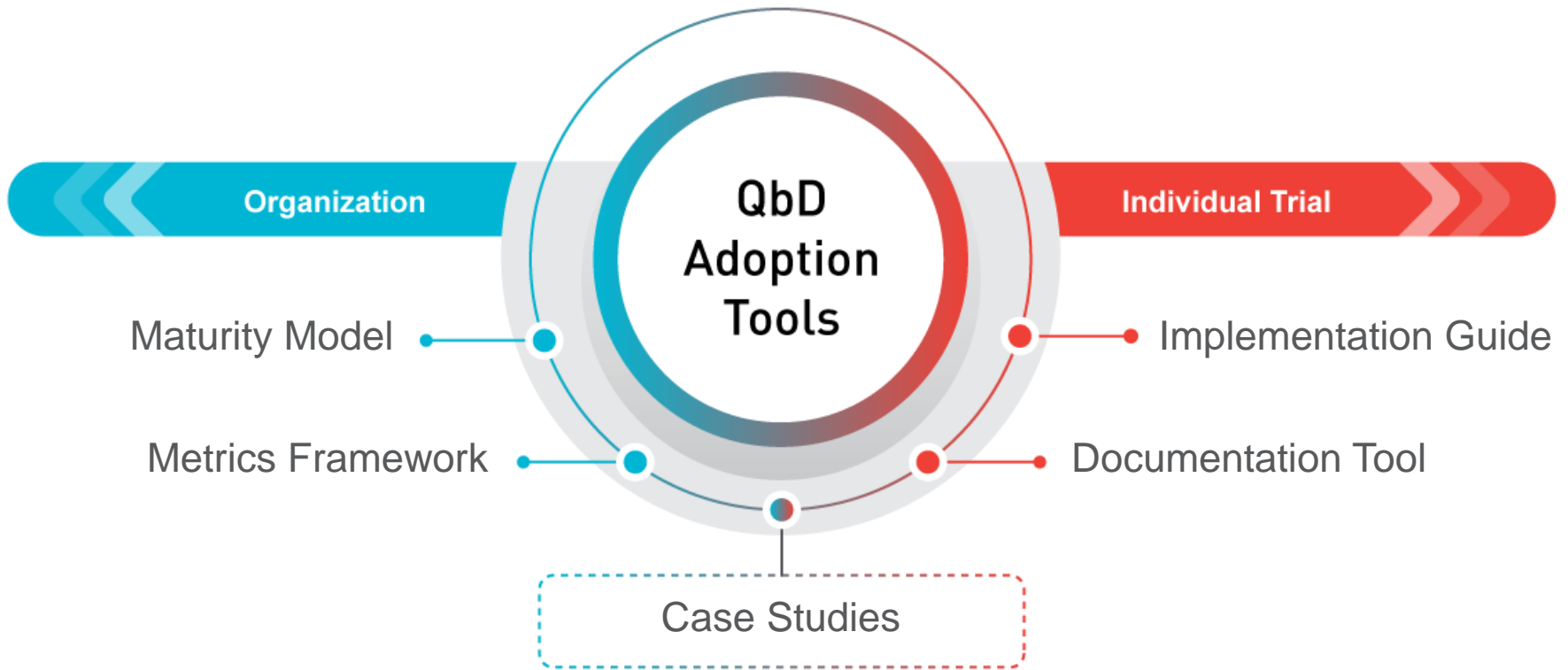
REFLECT



Closing Comments and Q&A

Pamela Tenaerts, CTTI





CTTI's Existing QbD Tools

- [Components for QbD Adoption](#)
- [Setting Expectations](#)
- [Team Recognition & Ownership of the Process](#)
- [QbD Principles Document](#)
- [Measurement for Individual Study Teams](#)
- [Perspectives for QbD Discussions & Potential Champions](#)
- [QbD Workshop Tools](#)



CTTI's [QbD Recommendations](#) are foundational to all tools.



QbD Adoption Findings

- Clinical trials ecosystem moving toward an **end-to-end approach** to proactively identifying and addressing risks to critical-to-quality factors
- Ideal to **start as early as possible**, but QbD principles can add value at any stage of study planning
- Mature implementation of QbD includes **engagement across internal functional roles and external stakeholders** (e.g., patients, sites, CROs)

Thank You!

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THANK YOU.



All resources discussed today are freely available at
<https://www.ctti-clinicaltrials.org/projects/quality-design>



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