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
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)

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

CTTI Staff
- Zachary Hallinan, Project Manager
- Laura Shannon, Communications Manager

Team Members
- Liz Adams (Quorum Review)
- Austin Allan (Kura Oncology)
- Keith Barber (Syneos Heath)
- Kousick Biswas (VA)
- Sabrina Comic-Savic (Novartis)
- Dan Cooper (UC Irvine)
- Ryan Fischer (Parent Project Muscular Dystrophy)
- Annie Fors (KUMC)
- Coleen Glessner (Alexion)
- Martin Hamilton (FDA/CDRH)
- Jan Hewett (FDA/CDER)
- Helen Howitt (Syneos Health)
- Irfan Khan (FDA/CDRH)
- Kerstin Koenig (BMS)**

- Prajna Kumar (Alexion)
- Martin Landray (U. of Oxford)
- Marion Mafham (U. of Oxford)
- Ann Meeker O’Connell (Vertex)**
- Jules Mitchel (Target Health)
- Hamid Moradi (UC Irvine)
- Bob Moroz (Consultant)
- Jamie Phalp (KUMC)
- Petra Rathje (Amgen)*
- Craig Reist (Duke)*
- David Rodin (Amici Clinical Research)
- Margaret Schneider (UC Irvine)
- Fergus Sweeney (EMA)
- Mary Taylor (BD)

*Former team member  /  **Former team leader
## Brief Agenda

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

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

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**Trial Design**

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

**Outcome:** Operationally feasible trial design

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**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

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

- 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

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

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

Proposed Critical-to-Quality Factor (CTQ)

If there are errors related to this proposed CTQ...

Can the primary study objectives still be achieved?

Will the safety of trial participants still be protected?

Is there a uniquely important consideration for this study?

Not Critical to Quality

Critical to Quality
Operationalizing the Critical to Quality Factors

Critical to Quality Factors (CTQs)

Specific Risks to CTQ

Strategies to Address Risks
(Via Trial Design and/or Oversight)

Example

High retention critical for primary efficacy analysis

4-6 hour site visits may increase dropout rates

Sites not near patients; may lead to high dropout rates

Remove assessments if not tied to primary or key secondary endpoint

Minimize site visits; use digital health technologies and tele-visit

Provide travel/logistics support for necessary site visits
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:

### Stakeholder Engagement

<table>
<thead>
<tr>
<th>Level 1</th>
<th>Level 2 Early</th>
<th>Level 3 Developing</th>
<th>Level 4 Implementing</th>
<th>Level 5 Optimizing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad hoc</td>
<td>Study design considers some, but not all, stakeholders’ needs</td>
<td>Study design identifies and considers all stakeholders’ needs; not all stakeholders directly engaged</td>
<td>Study design includes direct engagement with all stakeholders from earliest stages of study planning</td>
<td>Study design collaboratively considers needs of all stakeholders</td>
</tr>
</tbody>
</table>

### Critical-to-Quality Focus

- Protocols include data collection not necessary for patient safety or credibility of findings
- Critical-to-quality factors (CTQs) not formally identified
- Operational implications of protocol not fully considered

<table>
<thead>
<tr>
<th>Level 1</th>
<th>Level 2 Early</th>
<th>Level 3 Developing</th>
<th>Level 4 Implementing</th>
<th>Level 5 Optimizing</th>
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<tbody>
<tr>
<td></td>
<td>Data collection considered against study objectives, but non-essential endpoints and assessments remain</td>
<td>All endpoints and assessments considered against scientific rationale, but other factors may still drive decisions</td>
<td>Study design process enforces strong justification for any study endpoints and assessments beyond the most fundamental</td>
<td>Study design is as simple as possible, with complexity proportionate to objectives</td>
</tr>
<tr>
<td></td>
<td>CTQs and associated risks to study quality discussed, but not systematically addressed</td>
<td>Formal process in place for identifying and addressing CTQs</td>
<td>CTQs systematically identified and addressed in protocol design, operational planning, and risk management and monitoring</td>
<td>Protocol and supporting documents simplified and streamlined, and all protocol-specific training aligned with CTQs</td>
</tr>
<tr>
<td></td>
<td>Operational implications often not considered until protocol is near-final</td>
<td>Operational implications considered from early stages of protocol design</td>
<td>Study-specific risks proactively identified, updated and controlled throughout study lifecycle</td>
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- Critical-to-quality factors (CTQs) not formally identified
- Operational implications of protocol not fully considered
- Data collection considered against study objectives, but non-essential endpoints and assessments remain
- CTQs and associated risks to study quality discussed, but not systematically addressed
- Operational implications often not considered until protocol is near-final
### Current State for “Stakeholder Engagement” (example cont’d)

<table>
<thead>
<tr>
<th>Factors:</th>
<th>Level 1 Ad hoc</th>
<th>Level 2 Early</th>
<th>Level 3 Developing</th>
<th>Level 4 Implementing</th>
<th>Level 5 Optimizing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stakeholder Engagement</strong></td>
<td>Study designed with input primarily from protocol writing team</td>
<td>Study design considers some, but not all, stakeholders’ needs</td>
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<td>Study design includes direct engagement with all stakeholders from earliest stages of study planning</td>
<td>Study design collaboratively considers needs of all stakeholders periodically updating understanding of who the stakeholders are, across the research enterprise, and their current needs</td>
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<td>Protocols include data collection not necessary for patient safety or credibility of findings</td>
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Patients consulted via advisory boards, but not until protocol is nearing completion.
## Current State for “Critical-to-Quality Focus” (example cont’d)

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<thead>
<tr>
<th>Stakeholder Engagement</th>
<th>Critical-to-Quality Focus</th>
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</thead>
<tbody>
<tr>
<td><strong>Level 1</strong> Ad hoc</td>
<td>Protocols include data collection not necessary for patient safety or credibility of findings. Critical-to-quality factors (CTQs) not formally identified. Operational implications of protocol not fully considered.</td>
</tr>
<tr>
<td><strong>Level 2</strong> Early</td>
<td>Data collection considered against study objectives, but non-essential endpoints and assessments remain. CTQs and associated risks to study quality discussed, but not systematically addressed. Operational implications often not considered until protocol is near-final.</td>
</tr>
<tr>
<td><strong>Level 3</strong> Developing</td>
<td>All endpoints and assessments considered against scientific, but other factors may still drive data collection. Operational implications considered from early stages of protocol design.</td>
</tr>
<tr>
<td><strong>Level 4</strong> Implementing</td>
<td>Study design process enforces strong justification for any study endpoints and assessments beyond the most fundamental CTQs systematically identified and addressed in protocol design, operational planning, and risk management and monitoring.</td>
</tr>
<tr>
<td><strong>Level 5</strong> Optimizing</td>
<td>Study design is as simple as possible, with complexity proportionate to objectives. Operational implications considered from early stages of protocol design. Approaches to study planning has some overlap with QbD concepts, but QbD not formally applied.</td>
</tr>
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</table>

**Factors:**

- **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**: Protocols include data collection not necessary for patient safety or credibility of findings. Critical-to-quality factors (CTQs) not formally identified. Operational implications of protocol not fully considered. Approach to study planning has some overlap with QbD concepts, but QbD not formally applied.
## Identifying Desired Future State (example cont’d)

<table>
<thead>
<tr>
<th>Factors:</th>
<th>Stakeholder Engagement</th>
<th>Critical-to-Quality Focus</th>
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</thead>
<tbody>
<tr>
<td></td>
<td><strong>Current State</strong></td>
<td><strong>Desired State (End of 2021)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Level 1</strong></td>
<td><strong>Level 2</strong></td>
</tr>
<tr>
<td>Level 1</td>
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</table>
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

*Developed in collaboration with CluePoints*
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

<table>
<thead>
<tr>
<th>Example Metric</th>
<th>Formula</th>
<th>Desired Trend</th>
<th>Measurable At*</th>
<th>Related QbD Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Complexity – Endpoints</strong></td>
<td>(# Endpoints Defined in Protocol)</td>
<td>↓ Decrease</td>
<td>▶ Draft study concept, ▶ Draft protocol, ▶ Final protocol</td>
<td>Streamlining</td>
</tr>
<tr>
<td><strong>Percentage of Important Risks Mitigated by Modifying Study Design</strong></td>
<td>[(# of Important Risks Mitigated by Modifying Study Design) / (Total # of Important Risks Identified During Study Design)] x 100%</td>
<td>↑ Increase</td>
<td>▶ Draft protocol, ▶ Final protocol</td>
<td>Both</td>
</tr>
<tr>
<td><strong>Rate of Patient Enrollment</strong></td>
<td>(# Patients Enrolled) / (# Sites) / (Patient Recruitment Period)</td>
<td>↑ Increase</td>
<td>▶ Intervals until enrollment complete</td>
<td>Streamlining</td>
</tr>
<tr>
<td><strong>Rate of Important Protocol Deviations</strong></td>
<td>(# Important Protocol Deviations) / (# Patient Visits)</td>
<td>↓ Decrease</td>
<td>▶ Intervals during study conduct</td>
<td>Fewer ‘Errors that Matter’</td>
</tr>
<tr>
<td><strong>Rate of Missed Assessments for Key Endpoints</strong></td>
<td>(# Missed Assessments) / (# Expected Assessments)</td>
<td>↓ Decrease</td>
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<tr>
<td><strong>Patient Satisfaction with Study Participation</strong></td>
<td>Average (Net Promoter Score)</td>
<td>↑ Increase</td>
<td>▶ Early/mid study conduct, ▶ Study closeout</td>
<td>Streamlining</td>
</tr>
<tr>
<td><strong>Rate of Avoidable Protocol Amendments</strong></td>
<td>(# Avoidable Substantial Protocol Amendments During “Active” Phase of Study)</td>
<td>↓ Decrease</td>
<td>▶ Study closeout</td>
<td>Both</td>
</tr>
<tr>
<td><strong>Number of Major and Critical Audit Findings</strong></td>
<td>(# Critical Audit Findings) + (# Major Audit Findings)</td>
<td>↓ Decrease</td>
<td>▶ Study closeout</td>
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<td><strong>Percentage of Important Risks Mitigated by Modifying Study Design</strong></td>
<td>[(# of Important Risks Mitigated by Modifying Study Design) / (Total # of Important Risks Identified During Study Design)] x 100%</td>
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</table>
# Reduced Rate of Important Protocol Deviations

Measurable at intervals during study conduct

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
<th>FORMULA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of important protocol deviations per patient visit</td>
<td>Metric = (# of Important PDs) / (# of Patient Visits)</td>
</tr>
</tbody>
</table>

### # 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
Closing Comments and Q&A

Pamela Tenaerts, CTTI
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!

Experts and stakeholders from across the clinical trials ecosystem, including patients and caregivers, made the QbD recommendations and resources possible.

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THANK YOU.

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

www.ctti-clinicaltrials.org