CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

November 2020

Quality by Design: An Overview and Considerations for Sponsorship

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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 Vertex Pharmaceuticals or the Clinical Trials Transformation Initiative.

Key Drivers for Change

If you are in a shipwreck and all the boats are gone, a piano top buoyant enough to keep you afloat that comes along makes a fortuitous life preserver. But this is not to say that the best way to design a life preserver is in the form of a piano top.

I think that we are clinging to a great many piano tops in accepting yesterday's fortuitous contriving as constituting the only means for solving a given problem.....

Operating Manual for Spaceship Earth, Buckminster Fuller;*1968*

Clinical trials are essential to the evaluation of promising scientific discoveries, but they are becoming unsustainably burdensome, threatening to deprive patients and health-care providers of new therapies and new evidence to guide the use of existing treatments.

Impediments to Clinical Research in the United States; J M Kramer, P B Smith, R M Califf, *Clinical Pharmacology & Therapeutics* (2012); **91** 3, 535–541

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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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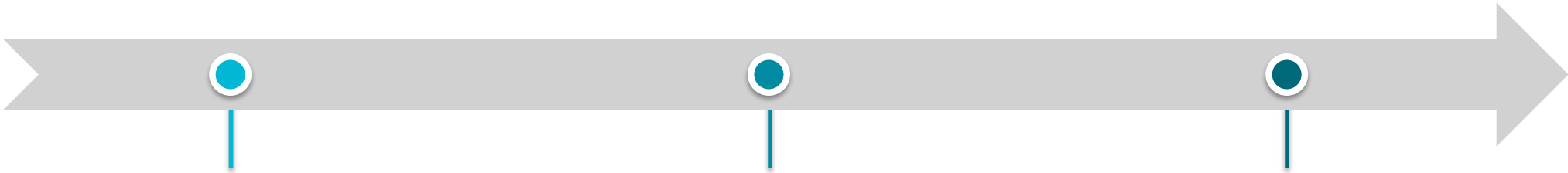
Evolution of Quality

CTTI Quality Projects: 2008 to Present



Monitoring

Key Insights:

- Quality cannot be 'monitored in'
- A "quality by design" approach is needed

Quality by Design

Key Outputs:

- Multi-Stakeholder recommendations
- QbD Toolkit to help apply principles

QbD Adoption

Addressing Gaps:

- Expanded Toolkit
- Concrete examples
- Organization-level planning and implementation tools

Reframing "quality" as the absence of errors that matter to decision making.

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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

“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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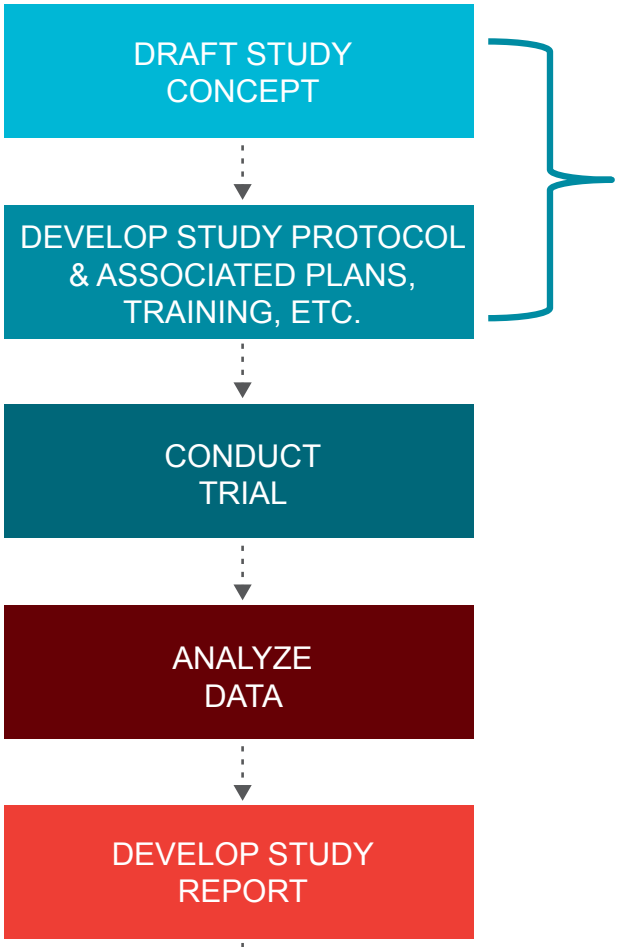
QbD Approach to **Study Design**



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)

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Critical to Quality Factors Principles Document

- Questions to promote
  - Proactive, cross-functional discussions
  - Critical thinking at the time of trial development
  - What is critical to quality for a specific trial
  - Events that might impede or facilitate achieving quality
- Not intended to serve as a
  - “Tick the box” exercise
  - “Checklist” to be completed in isolation
  - Substitute for experience and critical thinking
  - Quantitative risk assessment methodology
- Not all-inclusive

Exploring the Critical to Quality Factors

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

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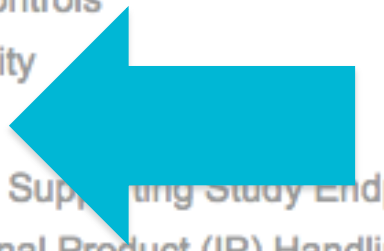
PROTOCOL DESIGN

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

Endpoints

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?

Outcome of Quality by Design

INTELLIGENT DESIGN

Optimal design to allow intended question(s) to be reliably addressed

Leverages insights from patients and other trial stakeholders to validate that the question and endpoints are meaningful

Clearly defined and rational number of endpoints, accepted by relevant stakeholders, and measured at appropriate timepoints.

Clearly defined population with sufficient numbers of participants for statistical validity

Procedures conducted and data collected are directly relevant to trial endpoints (efficacy and safety)

Accounts for variation in medical practice across intended sites

TAILORED IMPLEMENTATION

Oversight informed by knowledge of important risks not addressed through trial design

Monitoring focused on important risks to trial credibility, data integrity, and participant safety

Leverages centralized and statistical monitoring where feasible

Adapts oversight based on insights gained during trial conduct

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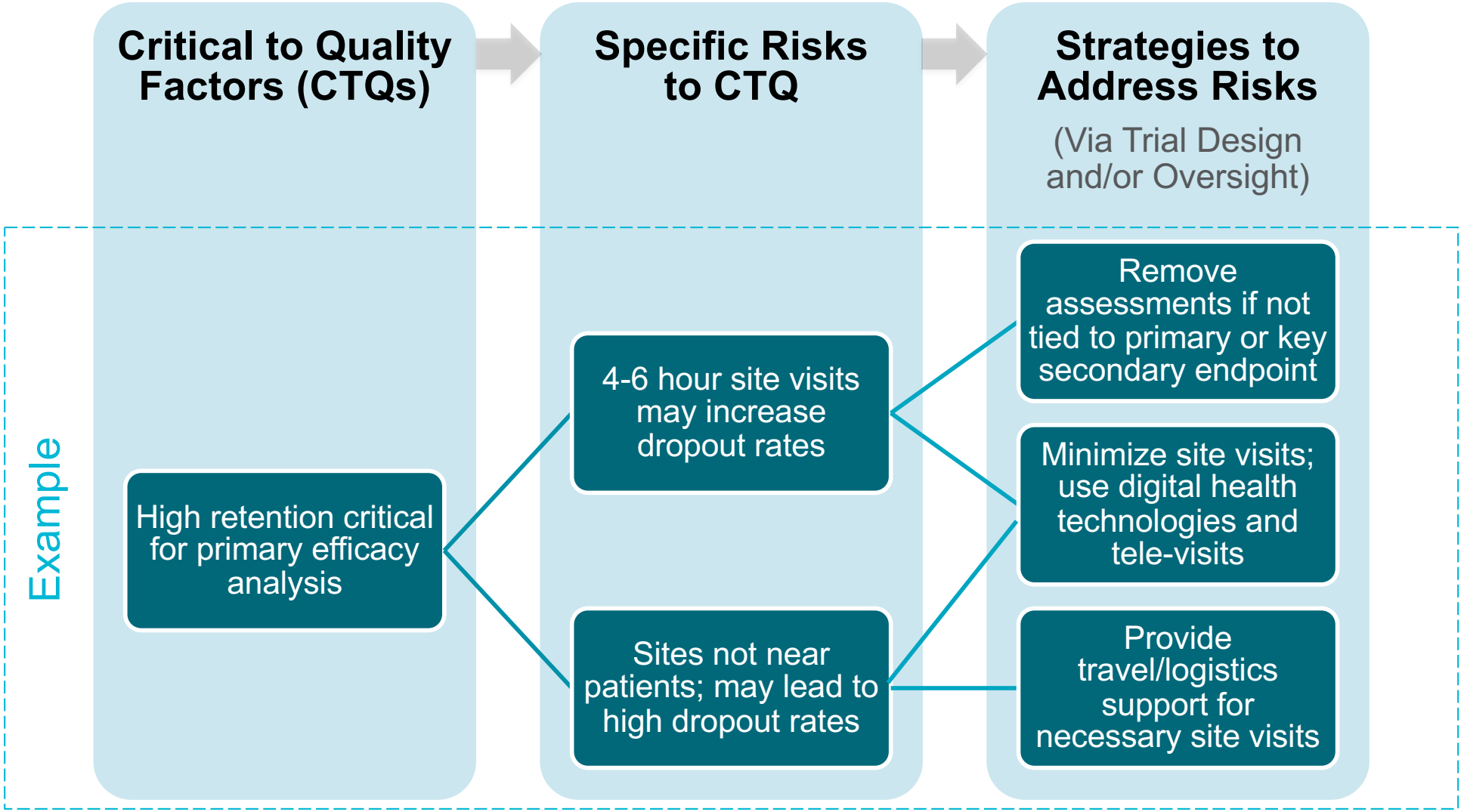
Operationalizing Quality by Design



Example from RECOVERY Protocol

5.1.1 Quality By Design Principles

In accordance with the principles of Good Clinical Practice and the recommendations and guidelines issued by regulatory agencies, the design, conduct and analysis of this trial is focussed on issues that might have a material impact on the wellbeing and safety of study participants (hospitalised patients with suspected or confirmed SARS-CoV-2 infection) and the reliability of the results that would inform the care for future patients.

The critical factors that influence the ability to deliver these quality objectives are:

- to minimise the burden on busy clinicians working in an overstretched hospital during a major epidemic
- to ensure that suitable patients have access to the trial medication without impacting or delaying other aspects of their emergency care
- to provide information on the study to patients and clinicians in a timely and readily digestible fashion but without impacting adversely on other aspects of the trial or the patient's care
- to allow individual clinicians to use their judgement about whether any of the treatment arms are not suitable for the patient
- to collect comprehensive information on the mortality and disease status

Source: https://www.recoverytrial.net/files/recovery-protocol-v3-0-2020-04-07.pdf

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Resources to Support QbD Implementation

All resources freely available from CTTI website at:

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

CTTI QbD Toolkit

LEARN ABOUT QBD

HOME - Toolkit - QBD (QUALITY BY DESIGN) TOOLKIT - 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.

CTTI'S QBD RECOMMENDATIONS

The CTTI QbD project has produced recommendations on the use and implementation of QbD.

QBD Toolkit

Learn About QBD

Teach Others About QBD

Adopt QBD

RESOURCES

- Principles Document (pdf)
- CTTI QbD Recommendations (pdf)
- Key Stakeholders (pdf)
- Maturity Model (doc)
- Metrics Framework (pdf)

Contact us for questions or comments on the QbD Toolkit

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

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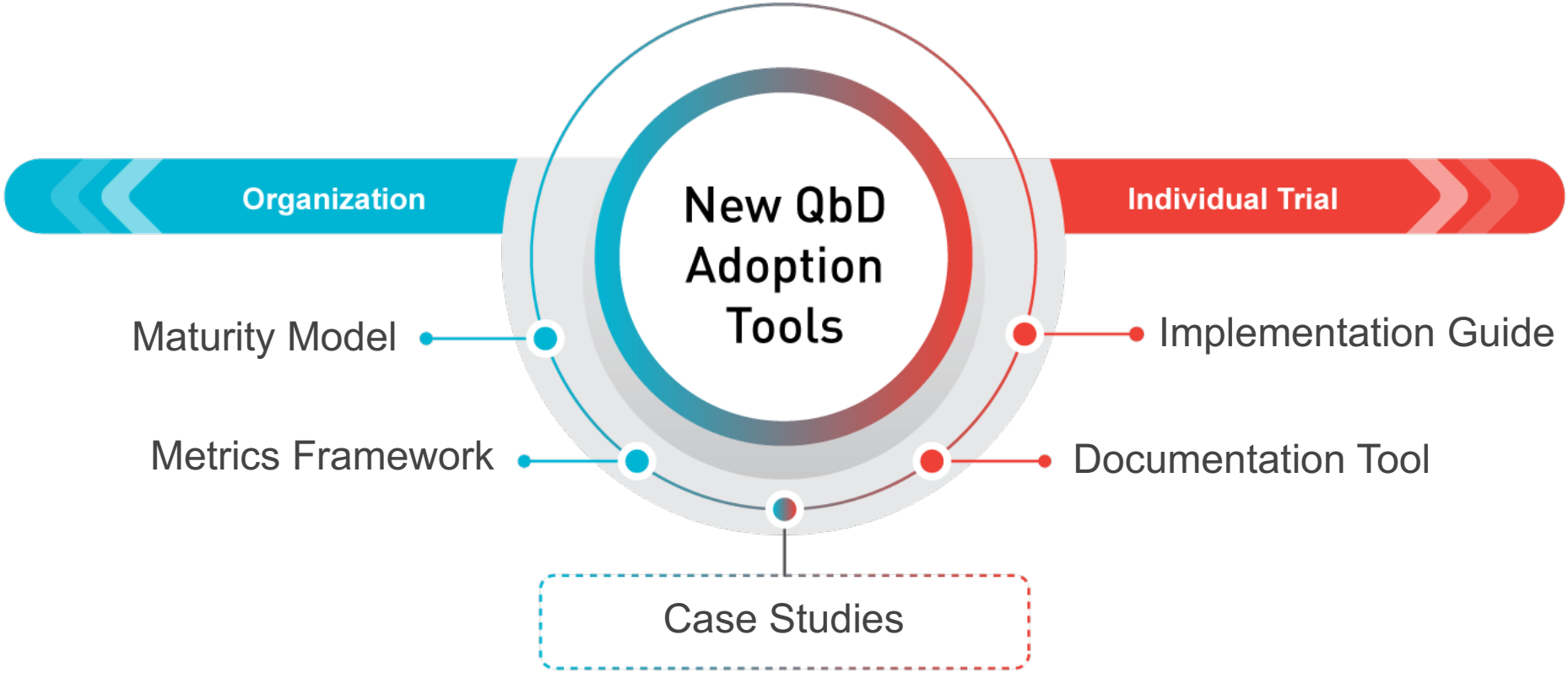


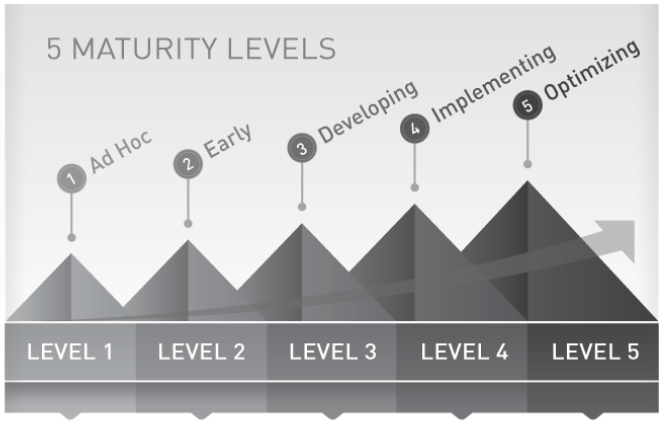
CTTI's Existing QbD Tools

- 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 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

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Example: Study Design Factors

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	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	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	All endpoints and assessments considered against scientific rationale, but other factors may still drive decisions Formal process in place for identifying and addressing CTQs Operational implications considered from early stages of protocol design	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	Study design is as simple as possible, with complexity proportionate to objectives Protocol and supporting documents simplified and streamlined, and all protocol-specific training aligned with CTQs Study-specific risks proactively identified, updated and controlled throughout study lifecycle

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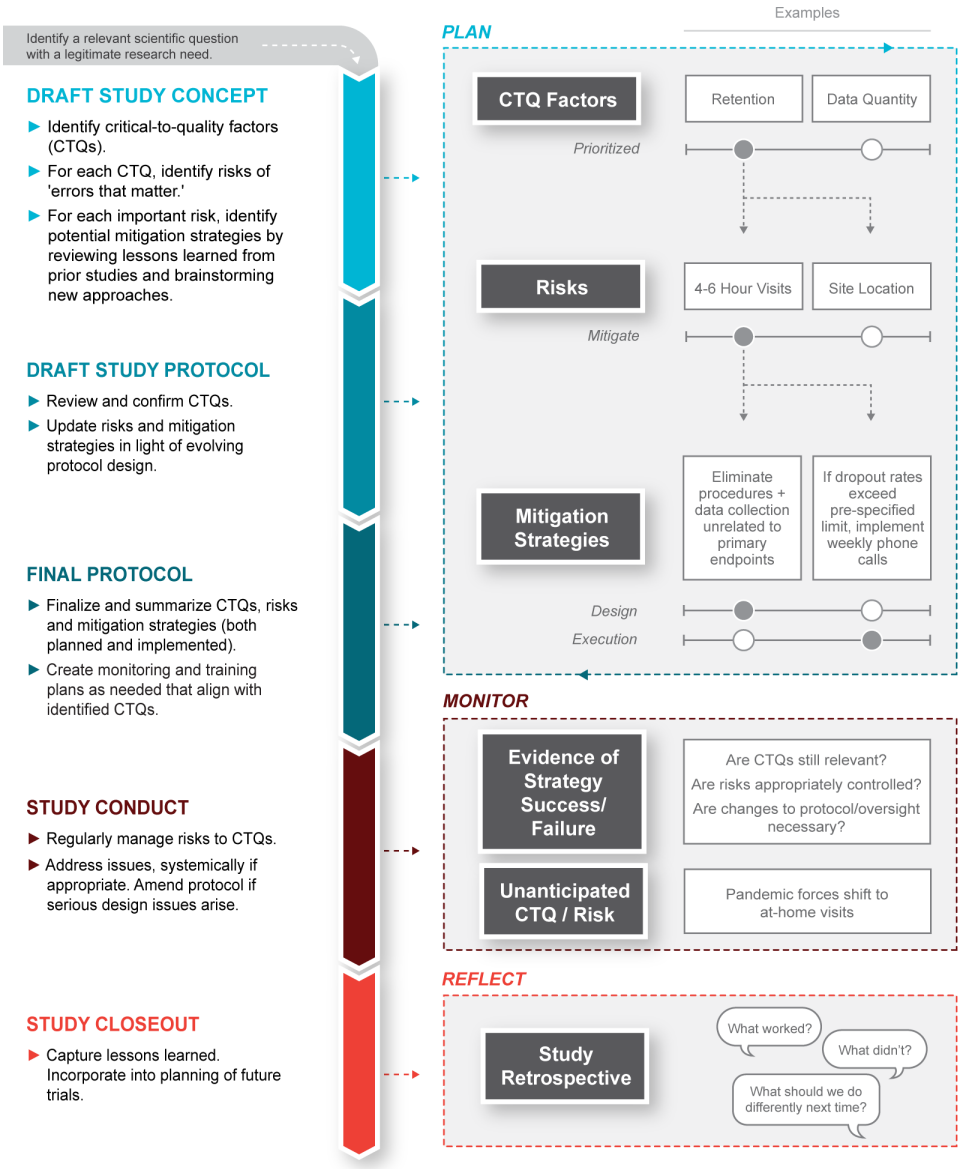
Current State **Desired State** (End of 2021)

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



Designed to Transition Knowledge from Initial Concept to Study Closeout

IDENTIFY & PRIORITIZE CRITICAL TO QUALITY (CTQ) FACTORS

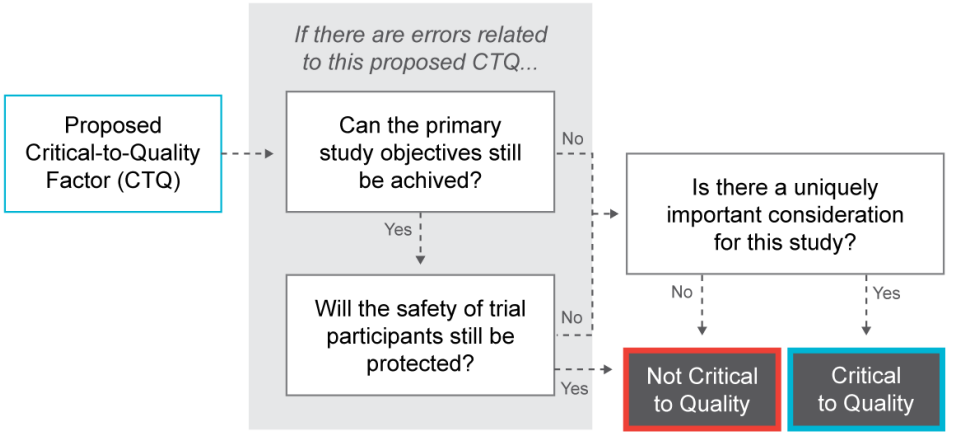
Early stages of study design should be patient and site-centric. Solicit input from them, as well as other key stakeholders.

Topic	Possible CTQ Factors	Rank	Specific Risk for Study	Mitigation Strategy
Protocol Design	Eligibility Criteria			
	Randomization			
Feasibility				
Patient Safety				
Study Conduct				
Study Reporting				
Third-Party Engagement				

IDENTIFY RISKS & MITIGATION STRATEGIES

For each selected CTQ, brainstorm what the most important risks are, and how these risks could be proactively prevented or mitigated. Note: there may be multiple risks per CTQ, and multiple strategies per risk.

Selected CTQs	Specific Risk for Study	Accept/Mitigate	Mitigation Strategy	Strategy Type	Strategy Status
Retention	Study visit may take 4-6 hours to complete	Mitigate Risk	Review all activities and look for opportunities to eliminate procedures and data collection unrelated to the primary questions of interest	Design	Implement
Retention	Study visit may take 4-6 hours to complete	Mitigate Risk	Implement additional retention interventions (e.g., weekly phone calls, study newsletter) if dropout rates exceed pre-specified limit.	Oversight	Undecided
Retention	Study length (>1 year)	Accept Risk	NA		
Retention	Study length (>1 year)	Accept Risk	NA		



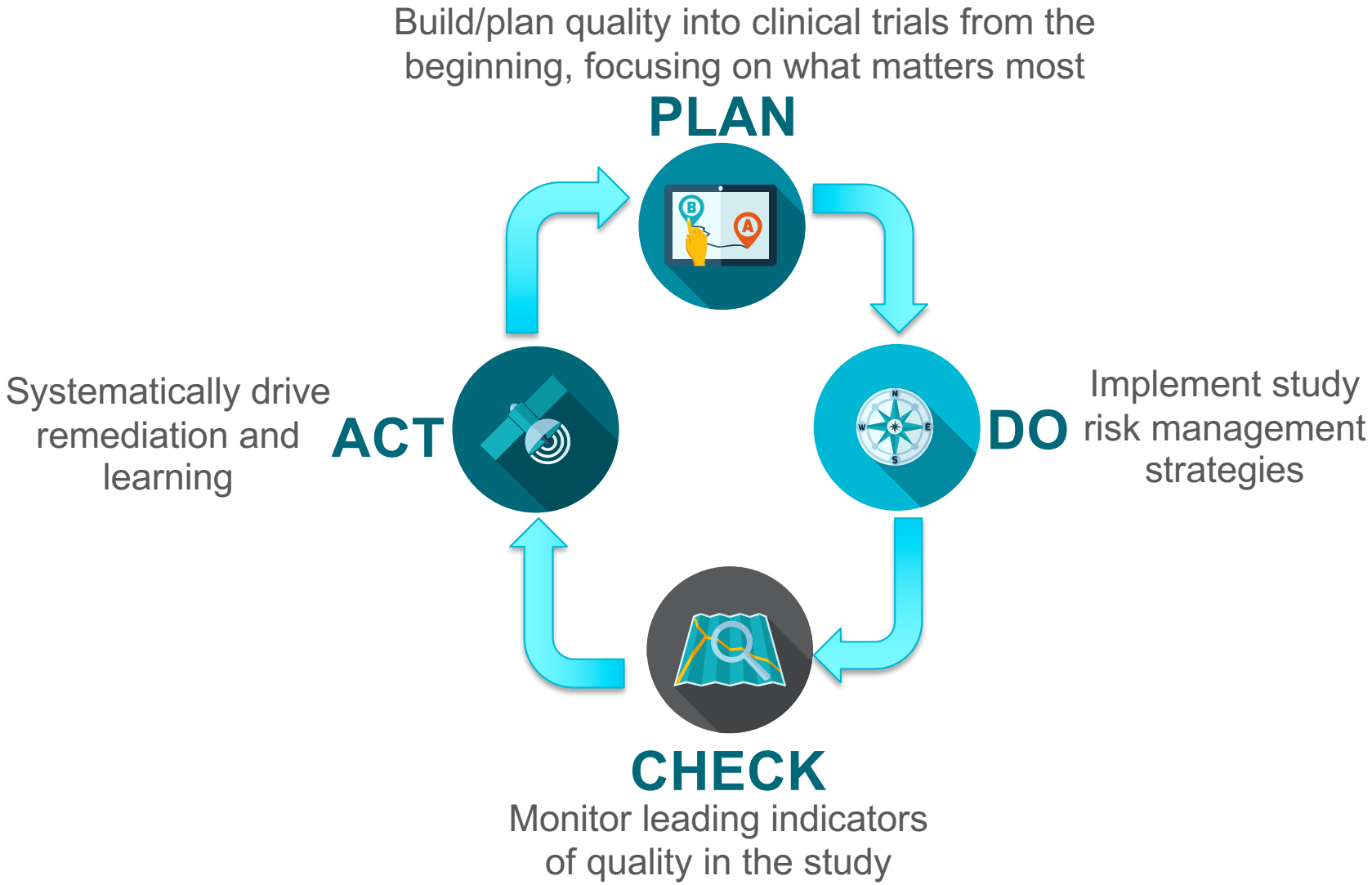
Example: QbD at UC Irvine-Implementation

- ***QbD Working Group composition-multidisciplinary***
  - **Core members:** Expert in informatics, Expert in statistical design, Recruitment expert, Regulatory expert, Senior study coordinator/Research nurse, Experienced clinical trial investigators.
  - **Ad-Hoc members:** Individualized based on each study.

QbD at UC Irvine-Implementation

- A 2-year pilot,
  - The goal will be to apply QbD principles over a 2-year period to selected clinical trials.
  - QbD team will meet with the PI and provide feedback/suggestions.
  - One study evaluated every 3 months.

QbD Implementation: Plan, Do, Check, Act



THANK YOU.

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