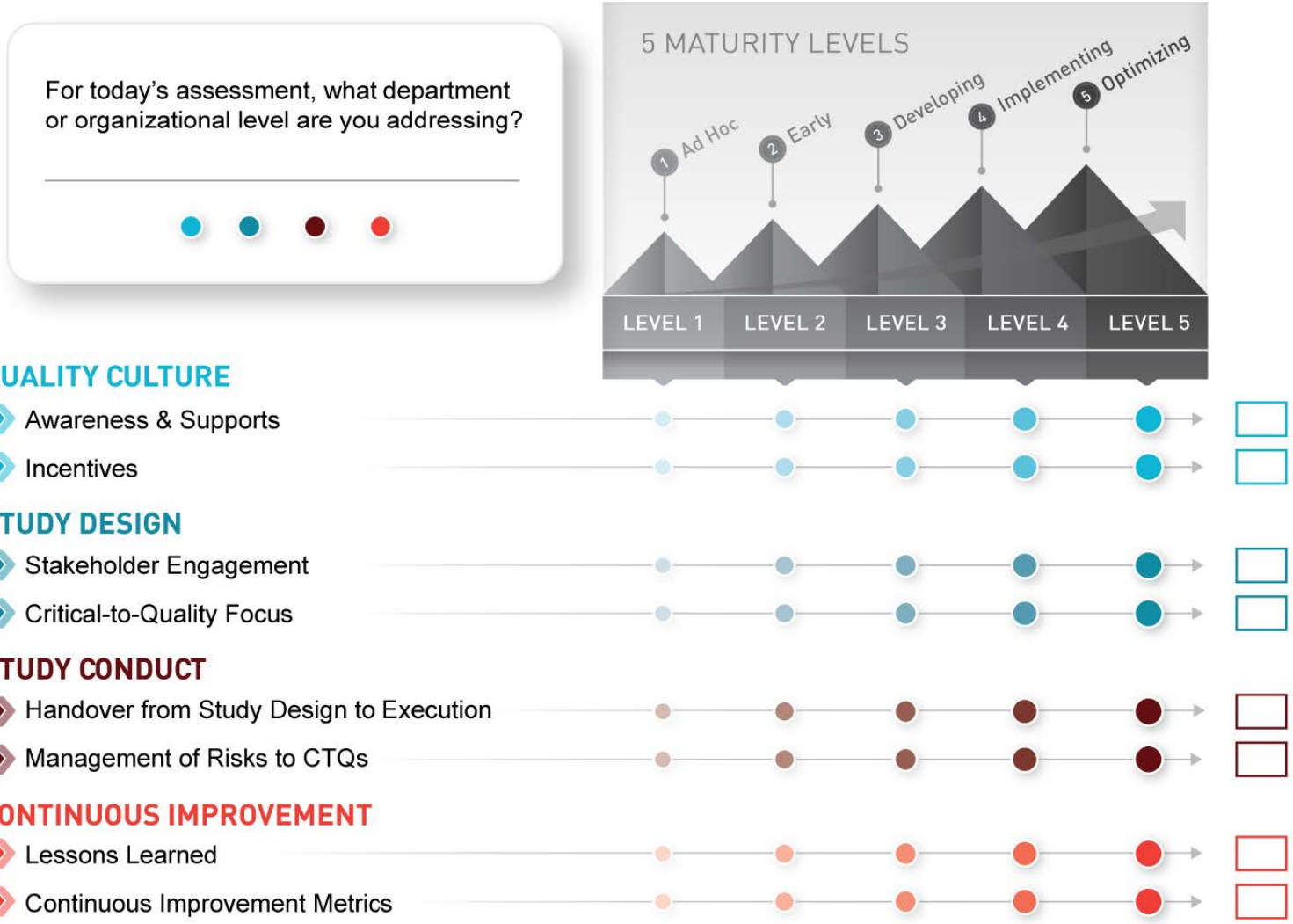
CTTI Quality by Design (QbD) Maturity Model

This Maturity Model can be used by research organizations to assess their current implementation of Quality by Design (QbD) for clinical trials, as well as to identify a desired future state. In this document are the Maturity Model itself (starting immediately below), as well as brief instructions, definitions and links to supporting resources. A brief walkthrough and scoring examples are also available. This tool is primarily aimed at organizations[1] that plan, conduct, and/or oversee clinical trials, including industry sponsors, CROs, academic research organizations, and patient groups.



[1] *For concision, the Maturity Model uses only the term "organization". Wherever this term is used, however, it should be interpreted to mean whichever level of the organization (the organization/company as a whole, a specific business unit, etc.) is being examined.*

Factors	**Level 1** Ad hoc	**Level 2** Early	**Level 3** Developing	**Level 4** Implementing	**Level 5** Optimizing
			QUALITY CULTURE		
Awareness & Supports	No QbD framework No individuals responsible for driving QbD implementation	Some awareness Piloting processes and supports (e.g., workgroups, trainings) Focal point identified, but role not fully defined or communicated	Broad awareness, leadership support Processes/supports established but not organization-wide Dedicated subject matter expert(s) assigned formal responsibilities for driving implementation	Awareness extends to partner organizations Processes/supports implemented across organization Subject matter expert(s) networked with designated contacts across internal and external stakeholders	QbD embedded in organizational culture and institutionalized, no longer requiring individual focal person Processes/supports periodically reviewed and enhanced via consultation with all stakeholders
Incentives	No formal or informal incentives for implementing QbD Incentives may reward the wrong behaviors	Piloting incentives for some elements of QbD (see Recommendations)	Incentives established for most (but not all) elements of QbD, and for most (but not all) relevant stakeholders	Incentives for all stakeholders encourage implementation of all elements of QbD	Incentives monitored for effectiveness, regularly reviewed and enhanced Incentives with unintended negative consequences have been eliminated
			STUDY DESIGN		
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

Factors	**Level 1** Ad hoc	**Level 2** Early	**Level 3** Developing	**Level 4** Implementing	**Level 5** Optimizing
			STUDY CONDUCT		
Handover from Study Design to Execution	Incomplete transfer of responsibilities to those responsible for study execution and oversight	Transfer is complete, but directive rather than interactive (thrown over the wall)	Transfer is complete and provides some big-picture understanding (but not always enough to facilitate problem solving)	Full transfer to all stakeholders in a way that facilitates problem solving (each role understands what it needs to do and why)	Full transfer via partnership model, including engagement from earliest stages of study and even program design
Management of Risks to CTQs	Quality management not tied to risks to CTQs	Risk-informed quality management loosely tied to CTQs Changes to protocol or trial oversight often not based on addressing risks to CTQs	Risk-informed quality management moderately tied to CTQs Some changes to protocol and trial oversight based on addressing risks to CTQs Continued relevance of CTQs sometimes assessed during study conduct	Risk-informed quality management directly and strongly, but not fully, tied to CTQs Most changes to protocol and trial oversight directly address risks to CTQs	Risk-informed quality management directly and fully tied to CTQs CTQs regularly assessed and risk mitigation strategies updated across study lifecycle All appropriate stakeholders engaged in decision-making
			CONTINUOUS IMPROVEMENT		
Lessons Learned	Informal review and dissemination of lessons learned at end of study	Study 'after-action' reviews QbD elements (e.g., right CTQs, appropriate mitigation strategies, unanticipated risks) Lessons learned do not consistently inform future studies	Lessons learned often inform future studies, but substantial barriers remain (e.g., data incomplete, siloed or difficult to access)	Lessons learned are systematically and collaboratively captured and shared across stakeholders Study design consistently incorporates lessons learned	Organizational culture, technology, and systems fully support rapid incorporation of lessons learned into quality planning of all future trials
Continuous Improvement Metrics	Quality of studies is inconsistently measured and difficult to predict	Some appropriate outcome and process metrics identified for monitoring QbD implementation at organizational level	Range of appropriate metrics tracked, though output not consistently used Study quality tending to improve	Quality consistently improving across partner organizations on meaningful metrics established with input from broad range of stakeholders	Metrics regularly reviewed and updated in alignment with evolving strategic plan for QbD implementation that incorporates all stakeholder needs and perspectives Consistent quality improvements over long term

ASSESSING MATURITY AND PLANNING QBD IMPLEMENTATION

One approach to using this tool is outlined below. The approach should be customized to best meet your needs and objectives.

Step 1: Select Unit of Assessment

Determine in advance whether you will be assessing the maturity of QbD implementation for the organization as a whole or a specific subset of the organization (e.g., a particular business unit). All scoring should reflect the typical or average experience for that unit of assessment, and the word "organization" in the Maturity Model itself should be interpreted as equivalent to the selected unit of assessment.

Example: Company X has decided to assess the QbD maturity of its Rare Disease Business Unit. Although the company as a whole is still developing processes for patient and other stakeholder engagement, the Rare Disease Business Unit already has strong practices in place for engaging with all stakeholders from the earliest stages of study planning. Thus, on the Stakeholder Engagement row of the Maturity Model, the Rare Disease Business Unit might be at a Level 4 or 5, even though the organization as a whole is only at a Level 2 for this Factor.

Step 2: Convene the Broad Range of Stakeholders

QbD emphasizes the value of bringing together the broad range of stakeholders to secure critical insights. The same is true when assessing maturity: consider bringing together all stakeholders[2] involved in study planning and execution—including external stakeholders, such as patients, sites, and CROs—and facilitate open dialogue[3].

Example: To help assess its QbD maturity and plan priorities for future implementation, the Rare Disease Business Unit organizes a daylong meeting that includes senior leadership, representatives from all key internal functions—including protocol development, clinical operations, and quality roles—and also invites stakeholders representing patients, sites, CROs and other operational partners they work with regularly. Meeting facilitation is carefully planned to ensure all voices are heard. The facilitators also decide to distribute the Maturity Model in advance in the form of an anonymous survey, both to provide additional opportunities for input by all stakeholders, and to help with planning a focused and efficient meeting.

Step 3: Assess Current Maturity

As a way to track progress, numerical scores can be assigned to represent an organization's current state on each Factor in the Maturity Model. For the selected unit of assessment, work through each Factor and select the "Level" (from 1 to 5 in the Maturity Model) that best reflects your current state.

Example: In reviewing the "Management of Risks to CTQs" row in the maturity model, the Rare Disease Business Unit determines that Level 3 is generally a good description of its current practices. Although they discuss some examples of substantially higher and lower maturity on this Factor, they ultimately decide those are outliers. However, there is also consensus that they are regularly approaching Level 4. Ultimately, they decide to assign a score of 3.5 for "Management of Risks to CTQs".

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[2] *To help identify relevant perspectives to include, please see Perspectives for QbD Discussions and Potential Champions.*

[3] *See, for example, https://hbr.org/2019/04/make-your-meetings-a-safe-space-for-honest-conversation*

Step 4: Set Future-State Objectives

The Maturity Model will provide greatest value when used not only to assess the current state of QbD implementation and diagnose issues, but also to develop plans for future implementation. Again, numerical scores can be assigned to reflect the maturity Level that the organization aims to reach on each Factor, within a stated period of time.

Example: As part of its daylong meeting on QbD maturity, the Rare Disease Business Unit discusses where it most needs to improve over the coming year. Knowing that it would be challenging to improve on all Factors simultaneously, given other business objectives for the year, the group decides to prioritize bringing "Critical-to-Quality Focus" and "Management of Risks to CTQs" to consistent Level 4 standards. The meeting is closed by assigning relevant individuals to draft plans for achieving those standards, and quarterly discussions with senior leadership are scheduled to review progress.

Considerations for Use

In using this tool, keep in mind:

- Discussions should engage all relevant stakeholders not only to arrive at a score for the current state of QbD implementation, but also to determine where to focus improvement efforts.[4]
- An organization may wish to modify the Maturity Model, for example by removing a Factor that does not apply. However, it is critically important to speak to all stakeholders touched by that Factor to get consensus on whether or not removing the Factor is warranted.
- An organization does not necessarily have to reach Level 5 on all Factors to successfully implement QbD. More importantly, focus on incremental and iterative improvement over time, with plans in place to evaluate progress and re-prioritize areas for improvement at regular intervals.
- Ultimately, the scores assigned are much less important than the discussions that lead to those scores.

[4] *See, for example, this case study from the UK government explaining the stakeholders and specific meeting facilitation practices used in working with a different maturity model: https://transformingtogether.blog.gov.uk/2019/01/15/how-people-are-using-the-7-lenses-maturity-matrix/*

Supporting Resources: Maturity Model Definitions and Implementation Tools

The table below provides additional information and links to resources that may be helpful in using the Maturity Model to assess current implementation of QbD and to work towards a desired future state.

QUALITY CULTURE

Factor	Definition	Related CTTI Resources
Awareness & Supports	Includes the extent to which there is awareness of QbD across the organization, support for implementation of QbD principles at a leadership level, and the identification of a focal point or subject matter expert to drive implementation. Note that the focal point may start as an individual or small group, and evolve to a disseminated model in which quality is embedded across organizational functions.	To help increase awareness and understanding of QbD, see the range of resources available for learning about QbD, including high-level recommendations, a PowerPoint overview, and overview publication. Resources available to help adopt QbD include: ▶ Components of QbD Adoption: This resource describes the four key components needed for a successful QbD implementation. ▶ Setting Expectations: Setting expectations is essential for success. We provide some insights from others that have implemented QbD. ▶ Implementation Guide: This resource helps study teams plan and evaluate their implementation of QbD for an individual clinical trial, and serves as a guide to key QbD elements that will often be important to incorporate in trial planning and execution.
Incentives	The ways in which management culture is reinforced. Incentives can be positive or negative; can target both behaviors and end results; and can function at individual and group levels. Includes the range of social and behavioral factors that can motivate desired outcomes critical to the success of any QbD process.	

STUDY DESIGN

Factor	Definition	Related CTTI Resources
Stakeholder Engagement	What quality means to each relevant internal and external stakeholder (e.g., the various internal sponsor roles, CROs and other service providers, patients and patient groups, investigators and site personnel, regulatory agencies and payers, as appropriate).	See Perspectives for QbD Discussions and Potential Champions for considerations for internal and external perspectives that may be important to include in QbD discussions, as well as suggestions for identifying internal champions who can support implementation broadly. CTTI recommends engaging the "patient voice" from the beginning of any research and development program to improve trial design and execution, and has developed a range of recommendations and resources for realizing the value of effective engagement.
Critical-to-Quality Focus	The process of planning a study—protocol design, as well as related planning for operational considerations not captured in the protocol—including the identification of critical-to-quality factors and risk mitigation strategies.	Use the QbD Documentation Tool to help study teams capture and communicate decisions about what is critical to quality and how the most important risks will be addressed. This tool is also helpful in the Handover from Study Design to Execution (see below).

STUDY CONDUCT

Factor	Definition	Related CTTI Resources
Handover from Study Design to Execution	Ensuring that all stakeholders with responsibilities during study execution understand their role and its relationship to all other roles, as well as the critical-to-quality factors identified, risk-mitigation strategies, and controls.	QbD is about prospectively examining the objectives of a clinical trial and defining those factors that are critical to meeting those objectives. This requires thinking differently about clinical trials. CTTI has developed tools to support cross-functional and multi-stakeholder discussions to help identify these critical-to-quality factors, including: ▶ QbD Principles Document: This 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: 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. PowerPoint slide decks are also provided as templates to build your own workshop. Measurement for Individual Study Teams: Leverage Plan–Do-Check-Act Approach provides a high-level method for identification and oversight of quality performance during study conduct.
Management of Risks to CTQs	Ensuring that quality management activities – including risk-informed quality management – follows directly and logically from decisions about critical-to-quality factors and associated risks that were identified during study planning. This includes ongoing monitoring of risks to critical-to-quality factors that could not be eliminated during study design, and mechanisms for reviewing and improving processes while the study is underway.	

CONTINUOUS IMPROVEMENT

Factor	Definition	Related CTTI Resources
Lessons Learned	Emphasizes the importance of systematically conducting study 'after-action' reviews to assess decisions made during study planning, capture learnings from all stakeholders, and, most importantly, incorporate lessons learned (e.g., about protocol designs options to proactively mitigate important risks) into the design of future studies. Increasing maturity may require implementation of relevant knowledge management technologies and processes to store lessons learned in a way that is accessible to the right people when they need it, and that draws attention to the importance and relevance.	Encouraging study teams to use the self-evaluation elements built into the Documentation Tool and Implementation Guide are valuable ways capture lessons learned, and ideally will be supported by organizational processes and tools for storing and disseminating this information. The QbD Metrics Framework provides nine example metrics that help key stakeholders in clinical research organizations to self-evaluate QbD implementation and guide continuous improvement efforts. Such quantitative metrics should be used in conjunction with more holistic self-assessments such as the approach suggested by the Maturity Model, above.
Continuous Improvement Metrics	Includes identification, capture, and regular review of easily-interpretable data on the quality of clinical trials to ensure appropriate and effective implementation of QbD principles. Look to see trends toward improving quality over a series of studies. Ensure metrics are accessible to all relevant stakeholders (including, for example, CROs), and are used to guide data-informed approaches to continue driving improvements in study quality.	