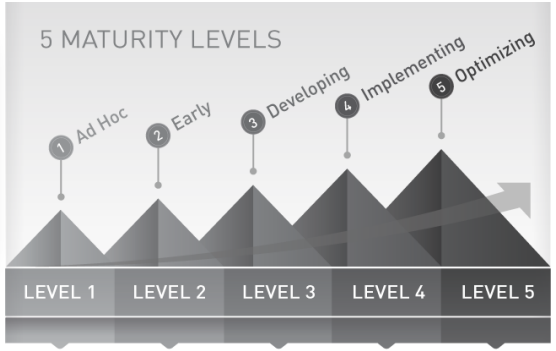
CLINICAL TRIALS TRANSFORMATION INITIATIVE

QbD Maturity Model Walkthrough and Scoring Examples

QbD Maturity Model Overview

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

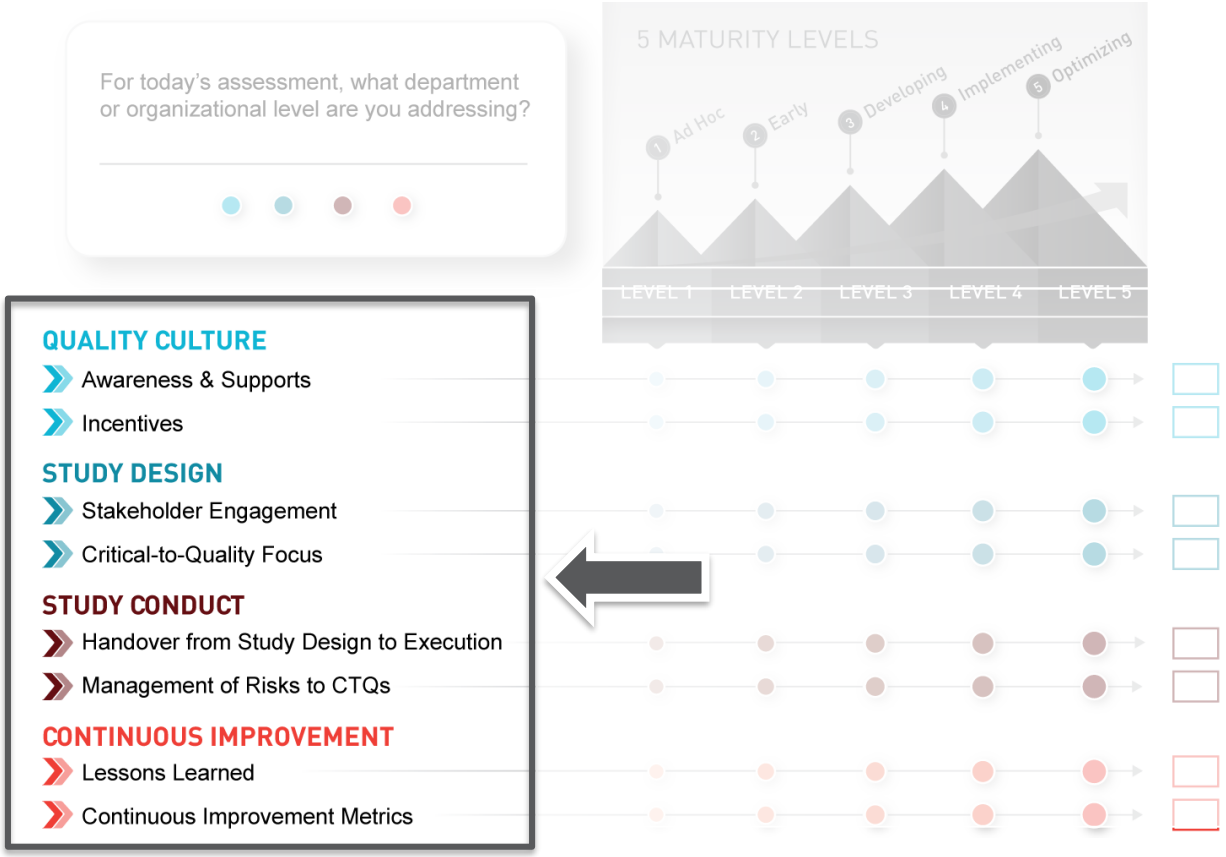
CONTINUOUS IMPROVEMENT
- Lessons Learned
- Continuous Improvement Metrics

CTTI has developed a Maturity Model to help organizations understand and implement a Quality by Design approach to clinical trials.

The next few slides will walk through the main elements of this Maturity Model one at a time.

Starting on slide 8, there are examples of how to use this tool to score QbD maturity and establish priorities for improvement over time.

8 Factors (Elements) of QbD



The Maturity Model focuses on eight Factors that, taken together, represent a complete implementation of Quality by Design for clinical trials.

The eight Factors in the Maturity Model are sorted into four Categories (Quality Culture, Study Design, etc.). These categories are directly aligned with CTTI's Recommendations for implementing QbD.

Each Factor Scored as Level 1-5

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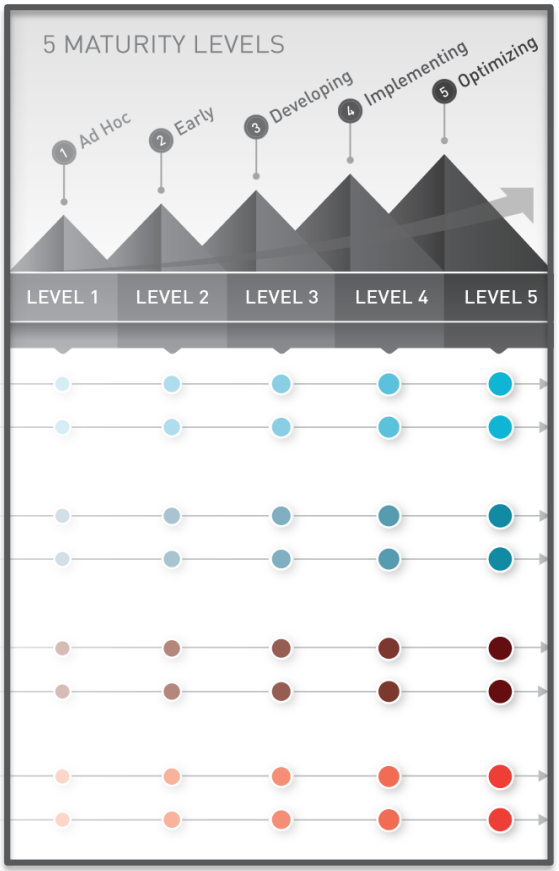

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Each Factor can be scored from Level 1 to Level 5.

In general:

- Level 1 implies little or no intentional implementation of QbD principles.
- Levels 2-4 imply increasingly complete and effective implementation.
- Level 5 describes an idealized state of complete implementation, along with continuous improvement efforts.

As shown on the next slide, each Level is described in text in an accompanying table.

Example: Level Descriptions for 2 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

This slide shows an example of how the Levels for two different Factors (Stakeholder Engagement, Critical-to-Quality Focus) are defined in the Maturity Model.

This is comparable to a 'scoring rubric'. An organization would look at the text in each Level and decide, for a given Factor, which best describes their current state.

In the full tool, similar text is provided for all eight Factors.

Maturity ‘Scores’ Can Be Tracked Over Time

The Maturity Model also includes an area to record scores for each Factor.

For each Factor, the Level that the organization is at becomes its ‘score’. For example, if an organization is at Level 3 on Incentives, then it’s ‘score’ for that Factor would be 3.

If helpful, an intermediate score cam be used. For example, if an organization has some elements of Level 3 and some of Level 4, they might decide on a score of 3.5.

Score the Whole Organization or Departments

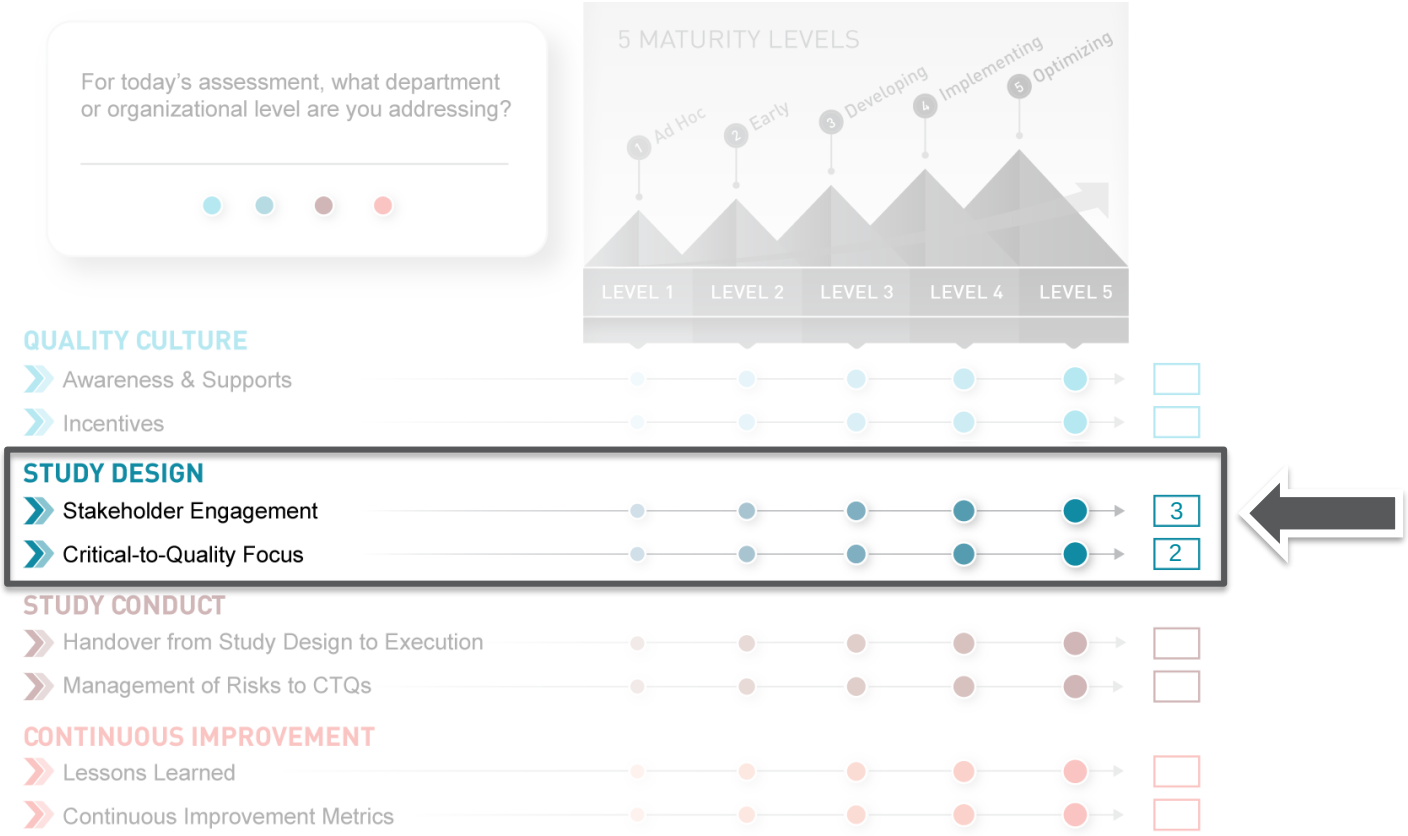
QbD maturity scores can be determined for the organization as a whole, or for particular business units or departments.

It is possible and even likely for different business units or departments to be at different Levels on each QbD maturity Factor.

So, when using the QbD Maturity Model, it is important to:

1. Start by determining what the unit of assessment will be (whole organization, particular business unit, etc.).
2. Score based on the typical or average experience for the selected unit of assessment.

Scoring Example: Study Design



This next set of slides provides an example of how an organization (or business unit, department, etc.) could use the Maturity Model to score its current implementation of QbD, as well as to plan a desired future state.

Here, the example organization has determined it is currently at Level 3 on Stakeholder Engagement, and at Level 2 on Critical-to-Quality Focus.

The next two slides flesh out the rationale.

Rationale for ‘Stakeholder Engagement’ Score

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	Stud inclu enga sta stud	r
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	Stud 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	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

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

In evaluating its maturity on Stakeholder Engagement, the example organization determined that:

- It does a good job of engaging the range of internal functions, and even sites and CROs;
- But it typically does not engage patients until too late in the study design process for their input to be optimally effective at helping to identify and avoid ‘errors that matter’.

Note: A list of potential stakeholders to engage in study design is available at this link.

Rationale for ‘Critical-to-Quality Focus’ Score

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 con scie but still Fo an CTC Ope imp con early stages of protocol design	Study design process enforces 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

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

In evaluating Critical-to-Quality Focus, the example organization determined that:

- Its processes are aligned in principle with QbD’s focus on proactively mitigating risks of ‘errors that matter’;
- However, work will be needed to ensure complete and systematic implementation of the key concepts (e.g., by updating SOPs and providing templates for capturing decisions about risk that are directly tied to critical-to-quality factors).

Identifying Desired Future State

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
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Current State

Desired State
(End of Next Year)

Finally, the example organization discusses where it would like to be by the end of the next year.

Here, the organization decided to prioritize moving both Stakeholder Engagement and Critical-to-Quality Focus to Level 4.

Similar discussions could be held for all eight of the Factors in the Maturity Model. See additional scoring examples on slides 13-19.

Considerations for Using the Maturity Model

Score based on what is typical
(Not best-case or worst-case)

The discussion is more important than the number

- Engage all stakeholders
- Facilitate open dialogue and honest assessment

Plan for **incremental and iterative improvement** over time

The full tool provides detailed instructions, but some of the most important considerations are identified here.

Perhaps most importantly, the Maturity Model is not a quantitative benchmarking tool for comparison between organizations, nor is it meant to provide audit or inspection standards.

Rather, it is meant to support meaningful discussion within an organization about implementation gaps and opportunities for continuous improvement.

Additionally, the goals for each organization may differ: not all will strive to be Level 5 in all areas, and an organization does not have to be Level 5 in all areas to be applying QbD.

Scoring Example: Quality Culture

Factors:	Level 1 Ad hoc	Level 2 Early	Level 3 Developing	Level 4 Implementing	Level 5 Optimizing
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, lead Proc esta Ded matt assi resp driving implementation	Awareness extends contacts across internal and external stakeholders	QbD embedded in ganizational culture d institutionalized, longer requiring dividual focal erson ocesses/supports eriodically reviewed d enhanced via nsultation 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

Early stages of formally implementing QbD

Continuing the scoring examples, here an example organization has determined that it is at Level 2 for Awareness & Supports.

It is still at early stages of implementing Quality by Design, but has made a commitment to increasing effectiveness by:

- Conducting educational workshops for study teams as they begin formally implementing QbD approaches
- Drafting processes for conducting multi-stakeholder discussions early in protocol development
- Identifying a QbD ‘champion’ who has leadership support for carrying implementation forward over time.

Scoring Example: Quality Culture

Factors:	Level 1 Ad hoc	Level 2 Early	Level 3 Developing	Level 4 Implementing	Level 5 Optimizing
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 s… QbD Reco…	Incentives	Incentives for all …lders …ge …ntation of all …s of QbD	Incentives monitored for effectiveness, regularly reviewed and enhanced Incentives with unintended negative consequences have been eliminated

Have not yet identified incentives to support QbD implementation

The example organization has determined that it is at Level 1 for Incentives.

One priority will be to reduce the ‘Christmas tree effect’ – the tendency for everyone involved in study design to add their own ‘ornament’ to the protocol, often resulting in studies that are overburdened, unfocused, and expensive. The organizations’ culture implicitly rewards anyone who is seen as having an impact on study design, while those who work to keep studies streamlined are rarely recognized.

The organization plans to establish recognition programs, highlighting success stories, and also plans to create individual employee objectives within its performance management system that are directly tied to QbD implementation.

Scoring Example: Study Conduct

Factors:	Level 1 Ad hoc	Level 2 Early	Level 3 Developing	Lev Impl
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 stak way pro un it ne why)
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 qual man direc stron fully, Most changes to protocol and trial oversight directly address risks to CTQs

List of CTQs, risks and mitigations provided, but rationale and operational implications not always clear

The organization has determined it is at Level 3 for Handover from Study Design to Execution.

Clinical operations staff and partners (CRO, sites, vendors, etc.) are consistently provided a list of identified critical-to-quality factors (CTQs), their associated risks, and mitigation strategies for the study.

However, because most of these staff do not directly participate in design-stage discussions, they lack full insight into why these CTQs are particularly relevant and don't fully leverage insights in their operational processes, plans and priorities.

The organization is exploring opportunities for broader engagement of operational partners in study design, as well as better documentation and trainings that concisely convey underlying rationale and potential operational implications.

Scoring Example: Study Conduct

Factors:	Level 1 Ad hoc	Level 2 Early	Level 3 Developing	Level 4 Implementing	Level 5 Optimizing
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 qual mod CTQ proto over addr CTQ Continued relevance of CTQs sometimes assessed during study conduct	address risks to CTQs	rmed anagement nd fully tied gularly d and risk n strategies across cycle All appropriate stakeholders engaged in decision-making

QbD and risk-based oversight are largely handled as parallel processes

The organization has determined it is at Level 2 for Management of Risks to CTQs.

Although it uses a risk-based monitoring approach, trial oversight plans leverage generic Key Risk Indicators and Quality Tolerance Limits that are not explicitly derived from identification of critical-to-quality factors relevant to a specific study.

The organization would like to reach a level of maturity at which study teams design targeted monitoring and other oversight plans to proactively address those risks to critical-to-quality factors (CTQs) that could not be eliminated by changing the study design.

Processes will also be put in place to regularly assess the continued relevance of CTQs, and the appropriateness of associated risk mitigation strategies, during study conduct.

Scoring Example: Continuous Improvement

Factors:	Level 1 Ad hoc	Level 2 Early	Level 3 Developing	Lev Imp	
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)	Less syst colla can Stud cons inco learn	
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	Qua impr parti on n metr with range of stakeholders	incorporates all stakeholder needs and perspectives Consistent quality improvements over long term

Strong commitment to ensuring each study learns from those that came before, but technological and cultural barriers need to be addressed

The organization has determined it is at Level 3 for Lessons Learned.

It has put processes in place to document decisions made during study design about critical-to-quality factors and associated risks, as well as to review and assess these decisions at the end of each study. These lessons learned are consistently captured in a standard format (study team decision log) that facilitates understanding by all functions/roles (not just Quality), including individuals not involved with the study.

However, this information is not on a central, easily accessible repository; it typically is not shared with operational partners such as the CRO; and in the rush to enroll the first patient, study teams often fail to review this information in planning their trial.

Scoring Example: Continuous Improvement

Factors:	Level 1 Ad hoc	Level 2 Early	Level 3 Developing	Level 4 Implementing	Level 5 Optimizing
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	Qua impr partı on m mu rang stak	

Good metrics in place, though primarily internally focused and not always used appropriately

The organization has determined it is at Level 3 for Metrics.

It has identified a reasonable set of metrics that are relevant to Quality by Design, feasible to track via an organizational dashboard, and are being reviewed at intervals by organizational leadership.

As a result, implementation of QbD is becoming more consistent, and the quality of the organization's studies has been improving.

However, these metrics are not shared with operational partners and not designed to help operational partners improve. There are also times when the organization uses the metrics inappropriately, such as setting expectations with study teams that all studies should be completed faster than the historical average.