alimentiv™

Quality by Design

Integrating QbD in clinical trials

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List of abbreviations

CRO	Clinical Research Organization
CtQ	critical to quality
CTTI	Clinical Trials Transformation Initiative
FDA	BIMO FDA's Bioresearch Monitoring Program
GCP	Good Clinical Practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
QbD	Quality by Design
QMS	Quality Management System
RBQM	Risk-Based Quality Management

1. Introduction to Quality by Design (QbD) and its importance in clinical trials

Selecting a reputable Clinical Research Organization (CRO) to trust with your clinical trial is a crucial decision that impacts the efficiency, quality, and value of the trial outcomes. Not all CROs share the same level of commitment and investment in the journey toward quality and continuous improvement.

Evaluating a CRO's dedication to quality requires a close examination of its alignment with Quality by Design (QbD) principles and how these are integrated into the way they do business. A CRO's commitment to quality, as reflected in its Quality Management System (QMS) framework, is a pivotal success factor in clinical trials amidst an evolving regulatory landscape. With the implementation of revisions to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E.8 R1 (2022) and E.6 R3 (2024) guidelines, having a robust QbD position makes a CRO stand out.

Understanding whether your chosen CRO is adequately prepared to meet these evolving regulatory requirements will help you make an informed decision that can impact your clinical trial success.

2. Understanding QbD in clinical trials

QbD is a transformative approach that reshapes how sponsors design and manage trials. ICH describes QbD as a systematic approach to evaluating, understanding, and refining drug development to focus on what affects critical quality attributes. That focus helps sponsors establish a viable strategy, taking into account research and experience to date, innovation, and compliance requirements, combined with plans that enable the mitigation of risks and issues as they emerge.

QbD emphasizes a study's ultimate outcomes through the definition of critical to-quality factors, drawing attention to critical assessments/events and encouraging contingency planning based on thorough risk assessment. Applying QbD involves incorporating space for thinking, collaboration, and planning before implementing a project. Taking these steps facilitates improvements in all facets of a clinical trial, from study design and execution to reporting.

Box 1: Quality in the lens of QbD.

QbD defines quality as freedom from errors **'that are critical'**, such as errors in study conduct, data collection, and reporting that affect the study endpoints and errors that jeopardize a patient's rights or safety.

2.1 Significance of integrating QbD in clinical trials

Applying a QbD framework in clinical trials saves valuable time and resources. This starts by ingraining steps into practices and procedures that ensure a robust, systematic assessment of scientific and operational factors before starting a study. Doing so establishes a clear pathway to achieving:

- compliance to ICH E6 (R3) and ICH E8 (R1) regulatory guidance
- better protocol designs that incorporate stakeholder inputs, learnings, and risks to optimize successful outcomes
- fewer protocol amendments to correct design flaws
- faster regulatory approvals and finding-free inspections
- more reliable data delivered consistently and efficiently
- more well-constructed, effective mitigations when issues arise
- a greater percentage of effort focused on activities that have the greatest impact on outcomes (for example, shifting effort toward better oversight and support of lower-performing sites while reducing time overseeing high-performing sites)
- better learnings that improve the designs and plans of future studies

2.2 The aim of this white paper

Applying QbD in every aspect of a study enables the best path forward, with the least risk, in the shortest time, resulting in the greatest value for cost.

This whitepaper will discuss how QbD, as defined in regulatory guidance ICH E.8 R1 and E.6 R3, can be applied to the design and delivery of clinical studies.

3. Insights from regulatory inspections drive QbD

Regulators and industry partners have assessed the vast amount of data collected from trial inspections over the years and found that the same categories of findings have continued to emerge across the drug development industry despite the existence of well-oiled, corrective, and preventive action mechanisms. As a result, they have collaborated with the Industry on guidance intended to address systematic quality issues by refocusing attention on improving the study designs to deliver quality outcomes.

3.1 List of quality issues found by regulators

A summary of systematic issues identified includes the following:

I. **Inefficiency in quality control.** Despite intensive inspections and audits, the same issues continue to surface about the overall quality of study conduct and results, raising questions about the effectiveness of quality control measures.

II. **Protocol discrepancies.** Protocols always state an intention to adhere to ICH guidelines, but inspections and audits often reveal compliance issues with good clinical practice (GCP).

III. **Quality by chance.** The design of clinical trials is typically performed under time pressures by a few trusted subject matter experts without the involvement of stakeholders like patients, site investigators, and CROs who have pragmatic and often innovative insights. As a result, quality in protocols often appears to be by chance rather than deliberate design. The high number of protocol amendments seen by regulators indicates a lack of structured quality control processes.

IV. **Siloed stakeholders.** A clinical trial involves a great number of stakeholders, including sponsors, CROs, institutions, sites, and service and technology vendors. Best practices are not consistent across all stakeholders nor in all phases of trials, contributing to quality issues.

V. **Lack of transparency.** Tracing activities across stakeholders to their source is challenging, making issue identification, tracking, and resolution difficult.

VI. **Inadequate root cause analysis.** Limited root cause analysis limits the ability to address underlying issues and use learnings to make valuable improvements.

VII. **Demonstrable oversight.** With the broad and deep involvement of stakeholders in delivering a clinical trial, it is often challenging to determine the delegation of activities and who is maintaining oversight. Ensuring the integrity of the research and compliance with regulations remains a persistent challenge.

3.2 ICH regulations on clinical trials

ICH E6 - Good Clinical Practice was initially released in 1996. It establishes the principles for clinical trial conduct. E6 sets the framework for designing, conducting, recording, and reporting trials involving human participants and outlines stakeholder responsibilities.

The guidelines were renovated beginning in 2017 to reflect technology advances as well as the need for a more evidence-based approach based on scientific principles to running clinical trials. E6-R2 introduced the concept of Risk-Based Quality Management (RBQM) and recommended a risk-based approach to quality management in seven key steps: critical process and data identification and risk identification, risk evaluation, control, communication, review, and reporting.

The latest amendment (R3), released in May 2023, further enhances the quality and efficacy of trials by incorporating the QbD concept and definition of key critical to quality (CtQ) factors impacting trial quality to prevent errors that could undermine the reliability of trial results. The amendment provides a flexible framework for clinical trial conduct that encourages new trial designs and technological innovations, strengthens the risk proportionate approach, and includes adopting a 'fit-for-purpose' approach to trial conduct that supports conclusions.

ICH E8 R1- General Considerations for Clinical Trials was originally adopted in 1997. As a result of a modernization initiative, a revised guideline became effective in 2022 and provides an overall introduction to clinical development, designing quality into clinical studies with a focus on those factors CtQ study outcomes. It encourages careful planning to generate meaningful, reliable, and fit-for-purpose data that will facilitate results acceptance by regulatory authorities.

Key concepts introduced include:

1) Identification of CtQ factors to support the meaningfulness and reliability of trial results and to protect human subjects. CtQ factors are the most crucial aspects of generating reliable data and protecting research participants.
2) Flexibility in approach to address a broader range of trial designs and data sources
3) Need to cross-reference ICH guidelines when planning clinical studies

Box 2: Highlights of ICH requirements.

ICH E.8 R1 requires quality to be part of a clinical trial design that focuses on critical to quality factors.

ICH E.6 R2 addendum requires protocol risk assessment and ongoing risk management for every new clinical study.

3.3 Clinical Trials Transformation Initiative (CTTI) recommends four changes to the traditional QMS

In support of better quality in clinical trials through the adoption of QbD principles, the Clinical Trials Transformation Initiative (CTTI) has surfaced four valuable recommendations:

I. **Establish a culture of critical thinking.** Encouraging critical thinking and dialogue about quality beyond relying solely on tools and checklists. Reliance on checklists and inflexible "one size fits all" approaches undermine specific strategies and actions to effectively and efficiently support quality in a given study.

II. **Focus on essential activities**. Concentrating on activities critical to the study's credibility and patient safety, such as rigorous design, streamlining trial design, and deploying resources to identify and control errors with high impact.

III. **Engage stakeholders**. Involving stakeholders, including investigators and potential trial participants, in protocol development and quality discussions. For example, investigators and trial participants have valuable insights into the feasibility of enrolling patients.

IV. **Identify CtQ factors.** Identifying and reviewing critical-to-quality factors to develop strategies for supporting quality in critical areas.

A number of organizations have applied CTTI's QbD recommendations to design and conduct better clinical trials (box 3). This is encouraging for Sponsors and CROs that envision evolving to answer best important clinical trial questions that address the needs of the patients.

Box 3: A QbD case study per CTTI's recommendations.

The ASCEND Trial conducted by the University of Oxford (clinical trial identifier NCT00135226) offers a real-world example of QbD implementation per CTTI recommendations. This trial studied whether aspirin and/or omega-3 fatty acids reduced the risk of heart attacks and strokes in people with diabetes.

With QbD at the core of the trial design, 3 CtQ factors were identified in ASCEND (sample size, adherence to treatment, and patient retention), and resources were directed to address these factors. On the other hand, patient-reported outcomes replaced non-critical factors, such as in-person doctor visits were replaced with these visits.

4. QbD transformation at Alimentiv

Alimentiv is a clinical development organization focused on gastrointestinal (GI) diseases where we can make the most difference in accelerating drug development and addressing patient needs. One of our key enabling objectives is to be a quality-by-design organization. We set out to make QbD core to the way we work, ensuring that every procedure and action we undertake is evaluated through the lens of QbD principles.

Since early 2020, we have undertaken four strategic initiatives to move us forward on that journey.

These include

1) implementation of a QMS framework with QbD as its centerpiece,
2) implementation of an RBQM approach (Forte),
3) application of QbD principles to study design,
4) cultivation of a QbD culture.

Figure 1. Strategic initiatives to shift toward a proactive QbD organization.

We continuously refine our framework based on insights from each exercise.

4.1 Quality Management System with QbD at its foundation

Implementing QbD in clinical studies requires a systematic approach, starting with a robust framework at its core. Successful QbD implementation requires an organization-wide commitment to a structured, risk-based approach to clinical studies. At Alimentiv, we are applying QbD as a foundational principle of the QMS.

The intent is to assess procedures as they are conceived or come up for review from the perspective of ICH E8 (R1) guidelines. These procedures include the design, planning, conduct, analysis, and reporting of clinical studies. The QMS can also drive this critical thinking when assessing issues and audit findings and when developing preventions and risk mitigations.

Box 4: At Alimentiv, we apply QbD as a foundational principle of our QMS.

The five key elements of our QMS and touch points where we intend to drive QbD into the Alimentiv way of working include (figure 2):

Element 1: Quality Manual defining metrics for desired quality outcomes, quality policy, and objectives

Element 2: Document Management and Change Control

Element 3: Training Management

Element 4: Audit Management

Element 5: Issue Management

Figure 2: The 5 core Alimentiv QMS elements with QbD at the core.

4.2 Forte: The risk-based quality management system at Alimentiv

Alimentiv has built a robust Risk-Based Quality Management (RBQM) approach, **Alimentiv Forte**. Forte combines therapeutic area expertise with a philosophy of Quality by Design that proactively identifies, mitigates, and minimizes risk at the study level. This is supported by a 21CFR11-compliant technology solution that provides an integrated view of trial data from multiple sources using risk and performance indicators to drive real-time decision-making.

Forte is incorporated as a Good Clinical Practice expectation by ICH (see section 3). Since the adoption of the ICH E6 R2 addendum to Good Clinical Practice, protocol risk assessment and ongoing risk management are required for every new clinical study.

Forte focuses on early risk identification, prioritization, and control in clinical trials. Clinical trials are becoming increasingly complex in how data is collected. Forte allows study teams to understand what is going on at the study, site, and/or patient level and, from there, determine the appropriate next steps for action.

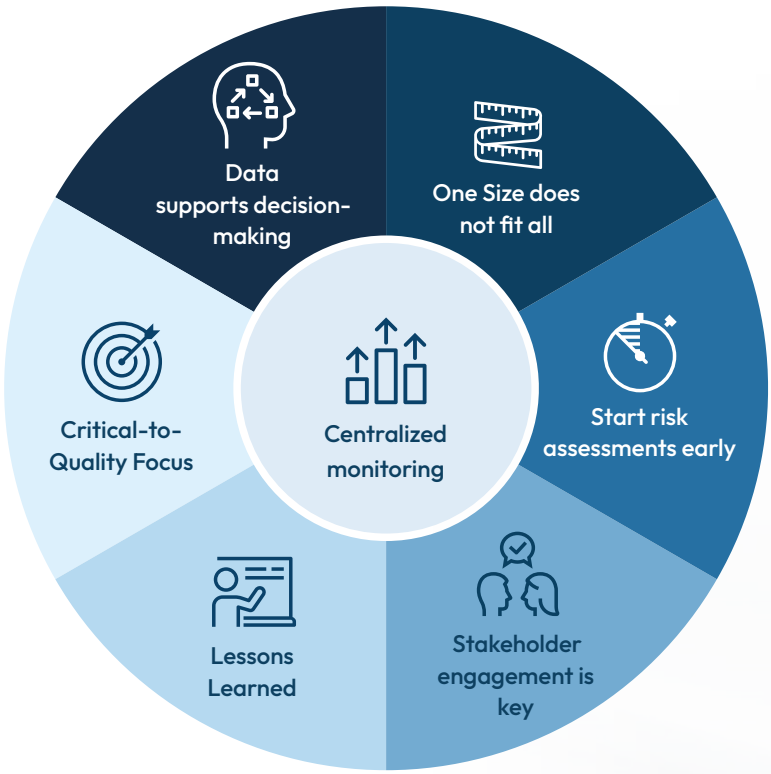
Our implementation of RBQM intends to surface and overcome challenges by transitioning to new, non-traditional ways of managing and monitoring clinical trials. This requires careful reflection and continuous attention to the differences between the traditional study management and monitoring approach and Alimentiv Forte (Table 1).

4.1.3 Table 1: Forte differs from the traditional clinical study management and monitoring.

Aspect	Traditional Approach	Forte RBQM at Alimentiv
Planning	Plans for regulatory timelines, less focus on planning for success.	Emphasizes planning for success with extra effort.
Issue Identification & Analysis	Address issues reactively as they emerge during the trial, limited root cause analysis.	Proactively identifies systematic issues and performs root cause analysis.
Improvement Efforts	Devote less time to implementing improvements for future studies.	Develops targeted improvements to address root causes.
Monitoring	Primarily, on-site monitoring with fixed schedules lacks focus on critical issues and limited supporting tools.	Primarily central monitoring prioritizes critical issues, supported by ZenQMS and OPRA tools to trigger deviation from CtQ factors.
Risk Identification & Mitigation	Relies on infrequent, routine monitoring with a reactive approach.	Emphasizes mitigation of predicted problem areas and proactive risk management.

Key considerations for successful adoption are defined in Figure 3:

Figure 3: Key considerations of Forte.



4.3 Applying QbD to study design

A robust trial design is essential to ensure a successful outcome. While designs may be medically and scientifically sound, traditional protocol development practices typically offered little involvement from stakeholders, including, for example, clinicians, patients, and CRO partners, resulting in unintended errors and avoidable risks during study conduct.

Applying QbD principles to Alimentiv's trial design process facilitates a more risk-based approach that focuses on aspects of the study that are critical from a participant safety, operational efficiency, and data reliability perspective. These insights help us identify critical data, processes, and risks that are valuable in creating plans that prevent critical errors.

At Alimentiv, we engage a cross-functional design team with deep indication-specific experience to provide insights on likely challenges and strategies for improving the study protocol. Stakeholder engagement, with a specific emphasis on participants and sites, is also crucial to a robust trial design and aligns with the call for patient and site-centric approaches in ICH E8. We are able to adapt site feasibility questionnaires to gather precise

feedback and incorporate key learnings into the protocol. Channels are also established to collect input from our patient advisory council, site network, and listening groups. Incorporating perspectives from participants and sites on symptoms, treatments, and disease concerns has the potential to reduce participant burden and improve engagement as well as reduce protocol amendments, which can be time-consuming and costly.

Box 4: Trial Design Case Study at Alimentiv.

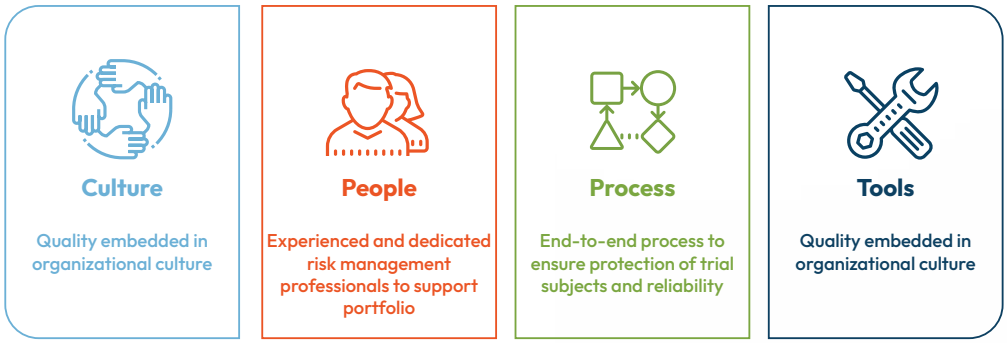
In an ongoing study, the team leveraged insights from the Sponsor's recently completed study in the same indication. They also applied their extensive experience from prior studies to proactively identify potential risks. They adapted a site feasibility questionnaire to gather specific feedback on these risks with the aim of reducing protocol amendments linked to avoidable issues.

The site feedback was valuable in helping Alimentiv to introduce key improvements to study plans, define and establish risk indicators around critical to quality factors, and develop robust risk mitigation plans aimed at reducing the need for protocol amendment and ultimately enhancing study efficiency and outcomes.

4.4 Cultivation of a QbD culture

Successful adoption of QbD is complex because it challenges fundamental ways of working embedded in the traditions of clinical study delivery. Of the four main change components that Alimentiv is addressing to achieve QbD –Culture of quality, People development, Processes that address CtQ factors and errors that matter, and Tools that enable collaborative planning, real-time visibility of study risks and risk management (figure 4), culture may be the most difficult because it challenges behaviors and training engrained across the industry over the past five decades. For example, a common behavior that pervades the management of clinical trials is 'urgency' to achieve milestones. While on-time delivery is important, before QbD, it was often done at the expense of 'critical thinking' that included stakeholder input to design a study with the greatest potential of success. Trialists were trained to accept zero study data defects and to spend substantial time checking and rechecking each data point against source documents regardless of criticality to study outcomes.

Figure 4: 4 components of adopting QbD.



E8 R1 section 3.3.1 states: "Creating a culture that values and rewards critical thinking and open, proactive dialogue about what is critical to quality for a particular study or development program, going beyond sole reliance on tools and checklists, is encouraged. Open dialogue can facilitate the development of innovative methods for ensuring quality." In short, ICH recommends a culture valuing critical thinking and open dialogue for quality improvement.

Adapting culture to move from the traditional approach ("This is the way we've always done it") to embrace new ways of working (more prospective planning and critical thinking of risks and mitigations) involves organization-wide awareness, re-training and safe opportunities to test, explore and learn from errors.

Specific to Forte, for example, we've engaged cross-functional teams to champion and embed the RBQM framework. New roles were created for oversight, risk management, and central monitoring. Some considerations for addressing the challenge of adapting culture to new ways include:

- **Overcoming resistance.** Any transformation faces resistance. Dialogues and education on quality and Forte are crucial to convince stakeholders of the need for change, emphasizing benefits like efficiency and quality.
- **Training and testing.** Comprehensive training, coupled with hands-on testing, provides confidence and fosters a culture of proactive learning and innovation.
- **Guidance and support.** Providing assistance and coaching as teams navigate the transition to new working methods ensures that the team is onboard and synchronized to embrace and adopt Forte.
- **Sustaining awareness with follow-up.** Consistent follow-up efforts reinforce awareness and comprehension of new practices and emphasize their importance.
- **Communicating new processes clearly.** Clearly articulating new standards and expectations ensures that everyone understands the organization's objectives and direction.

- **Measuring progress with clear metrics:** Measuring and tracking progress through relevant metrics allows Alimentiv to assess the effectiveness of the changes and make data-driven adjustments.
- **Continuous Improvement.** Implementing after-action reviews and feedback loops fosters continuous improvement, ensuring that Alimentiv remains adaptable and responsive to evolving challenges and opportunities.

5. Recap and conclusion

QbD is a crucial element in modern clinical research, and partnering with a CRO that understands the approach and has a framework in place to apply the principles can significantly influence a study's success. The impending implementation of ICH E.8 R2 regulations in 2024 underscores the importance of a robust QMS, protocol design process, and RBQM system. Evaluating a CRO's commitment to quality involves scrutinizing its alignment with QbD principles and the capability to apply these to clinical studies.

Alimentiv's investment in QbD reflects its commitment to improving study quality. Before choosing a CRO, assess their QbD readiness, resources, and track record. Ensure your CRO understands your niche risk assessment and has a trained team.

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