



Translating a Culture of Quality to Clinical Research Conduct: Expanding the Clinical Development Quality Framework

Michael Torok, PhD¹ · Leslie Sam, BA² · Jennifer Hebert, BS³

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Abstract

The International Council on Harmonisation E8 Guidance Revision 1 (ICH E8(R1)) calls for creating a Culture of Quality that “values and rewards critical thinking and open, proactive dialogue about what is critical to quality.” Across the biopharma landscape, clinical sites, sponsors, and service providers are working to translate this far-reaching guideline into working practices. This manuscript deconstructs key elements that comprise the critical thinking and open, proactive Culture of Quality “enablers.” In addition, maturity models are provided so readers can visualize what a Culture of Quality looks like in their clinical research organization. These provide examples of high performing cultures of quality and useful tools for teams or organizations to measure and evolve their respective quality cultures.

Keywords Culture · Quality · Open Dialogue · Critical Thinking

Abbreviations

AI	Artificial Intelligence	AVOCA	The Avoca Quality Consortium, a WCG company—A consulting and research firm in the life sciences industry, specializing in clinical research and quality improvement
ALCOA+	Principle that is crucial for ensuring data reliability representing the following principles (Attributable, Legible, Contemporaneous, Original, Accurate). The "+" sign indicates the inclusion of additional principles that further enhance data integrity. While variations exist, the "+" may represent principles such as (Complete, Consistent, Enduring)	BIMO	Bioresearch Monitoring Program
		CROs	Contract Research Organizations
		CTTI	Clinical Trials Transformation Initiative
		DIA	Drug Information Association
		GCP	Good Clinical Practice
		GLP	Good Laboratory Practice
		GMP	Good Manufacturing Practice
		GxP	Collective term used to refer to various Good Practice guidelines, with the "G" representing "Good" and the "P" standing for "Practice." The "x" is a placeholder for the specific letter(s) implied depending on the context. Common examples: GCP, GLP, GMP
		ICH E6(R2)	International Council on Harmonisation E6 Guidance Revision 2
		ICH E6(R3)	International Council on Harmonisation E6 Guidance Revision 3
		ICH E8(R1)	International Council on Harmonisation E8 Revision 1
		ICH	International Council on Harmonisation
		ISPE	International Society for Pharmaceutical Engineering
		ML	Machine Learning

✉ Michael Torok
torok.michael@gene.com

Leslie Sam
leslie.sam@lesliesamandassociates.com

Jennifer Hebert
hebert.jennifer@gene.com

¹ Global Head of Quality Assurance Programs at Roche/Genentech, 1 DNA Way, Suite 258A, South San Francisco, CA 94080, USA

² Leslie Sam and Associates, 2316 New Orchard Court, Sun City Center, FL 33573, USA

³ Roche/Genentech, 1 DNA Way, Suite 258A, South San Francisco, CA 94080, USA

PDA	Parenteral Drug Association
QA	Quality Assurance
QbD	Quality by Design
QMS	Quality Management System
SB	Serious Breach
SME	Subject Matter Expert
SQA	Society of Quality Assurance
TMF	Trial Master File

Introduction

Over the last decade, quality risk management practices within the pharmaceutical industry have evolved to focus on quality by design (QbD), risk-based approaches, and issue prevention [1–3]. One of the most influential guidelines driving this focus was the International Council on Harmonisation E6 Guidance Revision 2 (ICH E6(R2)) released in 2016 [4]. In parallel with similarly themed contemporary publications, this guidance provided a solid foundation for the clinical quality risk management practices that are still informing the work of industry-leading collaborations and thought leaders today.

In October of 2021, the release of ICH E8(R1) moved beyond earlier work to promote culture and the behaviors required to sustain it. General Considerations for Clinical Studies Sect. 3.3.1 “Establishing a Culture that Supports Open Dialogue,” describe these cultural considerations as well as critical drivers influencing quality as.

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 programme, going beyond sole reliance on tools and checklists, is encouraged. Open dialogue can facilitate the development of innovative methods for ensuring quality” [5].

The release of draft guidance ICH E6(R3) builds upon these themes and provides in-depth information for those seeking to explain and operationalize the ICH E6 and E8 requirements. Further, International Council on Harmonisation E6 Guidance Revision 3 (ICH E6(R3)) reinforced concepts introduced in ICH E8(R1), by fostering the idea of proactively building quality into trial design starting in the early planning stages and spanning both operational and quality groups.

The guidance of health authorities and published conceptual frameworks provided the initial impetus for individuals and teams to begin implementation of quality risk management practices. [6–16] However, most of these efforts do not fully consider the cultural impact of quality risk management when deploying these frameworks creating a missed opportunity to optimize these practices. Further, this may

even result in incomplete adoption by teams despite significant upfront investment of time and effort. In clinical development, there is extensive work required to create realistic translations of conceptual methodologies within the complexity of everyday operations. Therefore, it is not surprising when we sometimes forget that it is *PEOPLE* who design quality into investigational plans and apply risk-based methodologies to clinical development programs. It is *PEOPLE* who execute day-to-day clinical quality management system activities. It is *PEOPLE* whose everyday behaviors enhance or detract from the value of the clinical quality management enterprise. Safe and effective therapeutics are reliant on quality and quality is contingent on *PEOPLE*. Because of this interdependency, the culture of an organization will not only influence the success of quality risk management but also the eventual outcomes of clinical development programs. [17]

ICH E8(R1) requires quality be managed through a Culture of Quality with human behaviors such as Critical Thinking and Open Dialogue at its epicenter. This paper translates the regulatory expectation of a Culture of Quality into meaningful practices for clinical development that will underpin the operational aspects of ICH E6(R3).

Expanded Culture of Quality Strategic Enablers

In clinical research, the goals of trial participant protection and reliability of trial results are universally accepted as paramount to successful study conduct. In addition, while these clinical quality objectives are no doubt considered in the initial creation of organizational credos, mission statements, and quality policies, it is important to connect the lines between our overarching direction, our “True North,” and the conceptual Quality Management System (QMS) frameworks employed to govern daily operations. These frameworks include risk and issue management, measuring quality, management review, knowledge management, continuous improvement, and robust documentation to demonstrate the achievement of quality. They build on the foundations of regulatory requirements and thought leadership, lighting the path as we seek to define effective operational strategies. Along the way, we find gaps in quality, failures in oversight and poor outcomes that prove we have not fully identified or optimized these strategies. Moreover, while we can see where we want to go, we are missing the bridge between these conceptual QMS frameworks and our ultimate goals. This is where the utilization of four principal Culture of Quality Strategic Enablers provides a conduit to facilitate our journey to the other side (Fig. 1).

Each of the four Strategic Enablers comprises multiple behaviors and mindsets:

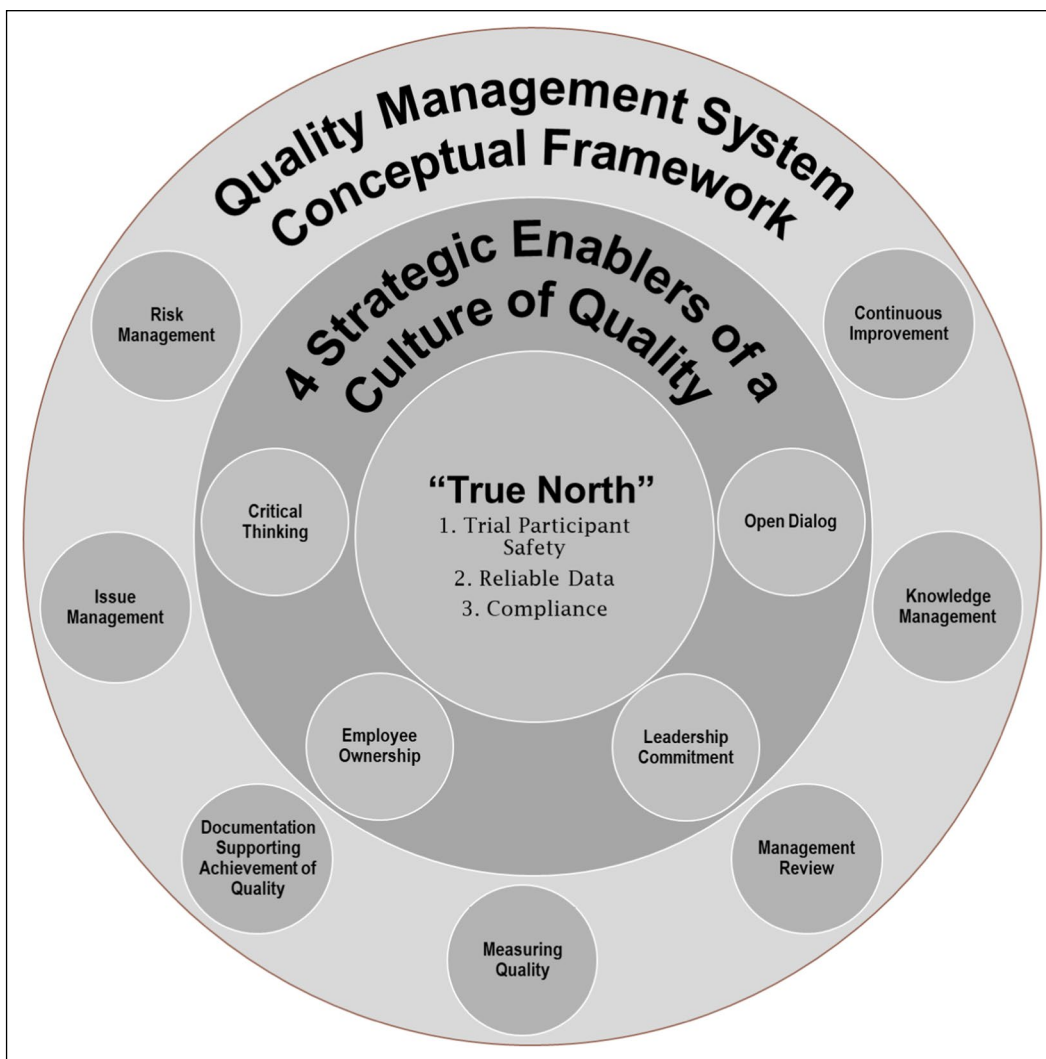


Figure 1 The Culture of Quality Strategic Enablers is the missing piece between the Quality Management System Conceptual Framework and “True North.”

Strategic enabler	Behaviors and mindsets	Strategic enabler	Behaviors and mindsets
Leadership commitment	A committed leadership will support <ul style="list-style-type: none"> • Creation of detailed quality goal development • Aligning rewards and recognition to culture • Clear accountability for quality performance 	Employee ownership	Employees will <ul style="list-style-type: none"> • Develop and maintain quality mindsets and values • Partner with Quality Assurance (QA) to foster an Open Dialogue and seek opportunities to improve Critical Thinking skills • Make certain that there is documentation to support the achievement of quality objectives
		Open dialogue	Open Dialogue is facilitated by <ul style="list-style-type: none"> • Accessing and exchanging data and information • Leveraging diverse intellectual capital • Quality Partnership and Team Engagement

Strategic enabler	Behaviors and mindsets
Critical thinking	<p>Critical Thinking is</p> <ul style="list-style-type: none"> • A learned competency taught through application of a systematic approach such as the “4As”: Ask, Analyze, Answer, Act • Relies on enhanced knowledge and expertise • Is developed through practice and offers opportunities for continuous improvement

The Open Dialogue and Critical Thinking Strategic Enablers are specifically called out in ICH E8(R1), while the remaining two (Leadership Commitment and Employee Ownership) are considered paramount for driving organizational dynamics to enable success. In this paper, we will describe and provide in-depth operational guidance for the realization of the first two (Open Dialogue and Critical Thinking) identified principal Culture of Quality Strategic Enablers.

Open Dialogue and Critical Thinking

It is important to recognize that Open Dialogue and Critical Thinking work together in a complementary fashion despite being independent concepts. A high performing Culture of Quality consistently demonstrates both Open Dialogue and Critical Thinking in tandem (Fig. 2).

For example, if we expect study teams to think critically about what to include in protocol amendments, it is imperative to provide access to the data and information relevant to the proposed changes as well as support proper analysis of feasibility and operationalization. If the development team fails to include the appropriate subject matter experts (e.g., medical, biostatistics, and quality—some of the intellectual capital for the study), to analyze information through their unique functional lens, there is a high risk of incomplete assessment(s) or poorly considered actions that will not fully address the needs of the study.

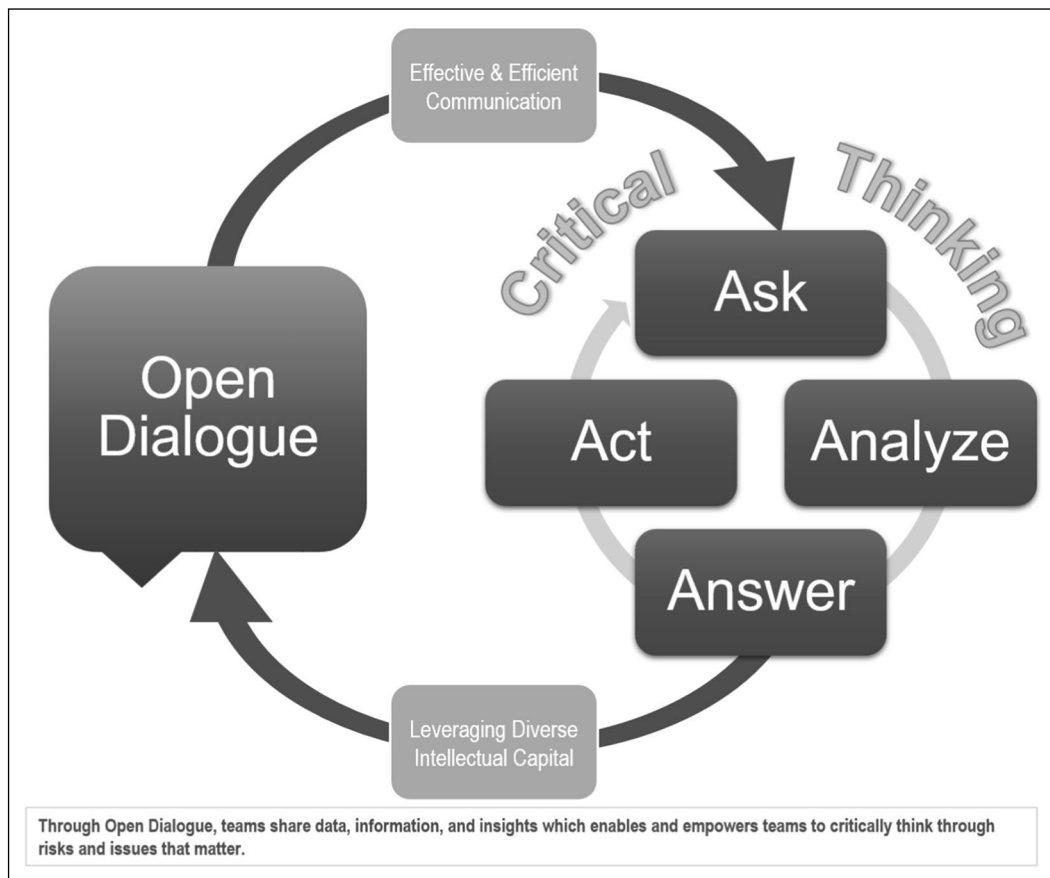


Figure 2 Relationship between Open Dialogue and Critical Thinking Strategic Enablers.

Open Dialogue: Data Access & Exchange

Data access and exchange is a critical factor leading to team success when implementing the Open Dialogue enabler. Poorly designed or overly complicated systems will prevent data from being viewed, openly shared, discussed, or examined, all of which will impair overall quality management practices (e.g., risk management). Such obstacles will frustrate even the most motivated teams seeking to evaluate the risk landscape when they find the systems managing data or creating analytics are too burdensome to use. Moreover, even with an intuitive user interface, a system that does not refresh at the cadence required to provide contemporaneous data creates a risk of inaccurate conclusions or failed analysis. In situations where a serious quality issue or serious breach (SB) occurs, an event may go unnoticed by the development team, and therefore, remain unmitigated, and unreported. This lack of information sharing across functions may leave time-sensitive activities such as SB expedited reporting at significant risk, leading to serious consequences downstream with health authorities.

Organizations with mature Cultures of Quality have user-friendly, quality performance systems, and analytics. Minimally, these mature organizations solve challenges around data interoperability to systematically produce and provide metrics across clinical development departments, vendor data, and QMS data to assess holistically the health of the clinical enterprise, identify process fragility, and predict quality outcomes. Further use cases for individual analysis and support using machine learning (ML)/Artificial Intelligence (AI) also exist; however, any use of data will always rely on the normalization of disparate data sets and the accuracy of underlying data. This leads to the important consideration and the imperative need to standardize data in the clinical development ecosystem. Given the volume of datasets, organizations should strive to have effective data governance models. Such models facilitate the linking and normalization of data so parties can discuss aligned data points while understanding inherent relationships between them.

The right systems and analytics should provide easy-to-mine regulatory, inspection, and quality intelligence. Examples of such critical systems components include:

- A regulatory intelligence system supports and manages effective and draft regulatory requirements.
- An inspection intelligence system is a database of inspection outcomes (how health authorities are interpreting regulations and measuring sponsor performance based on that interpretation).

- A quality intelligence system is a database of organizational QA and compliance data, metrics, analytics, and dashboards.

Overall, teams have greater opportunities for Open Dialogue, Critical Thinking, and proper documentation of both risks and mitigations when they have composite information from systems and intelligence databases. In other words, the capability to distill inspection, regulatory, and quality intelligence into usable inputs enables organizations to successfully metabolize knowledge and implement it in their day-to-day actions. If organizations do not democratize data through user-friendly systems, teams lack the appropriate perspective to manage quality according to the standards set forth by regulatory guidance.

Open Dialogue: Leverage Diverse Intellectual Capital

The second critical factor driving the value of Open Dialogue is the ability to have the right data, analytics, and knowledge management capabilities available to the right team members. Furthermore, these individuals must demonstrate competency in analyzing data or leveraging regulatory, inspection, and quality intelligence, to be effective when managing quality (e.g., quality risks and issues). Mature teams will continuously work toward mastery of these skills and learn from each other as well as subject matter experts when additional knowledge is required. As some experts will sit outside the immediate team's department or even organization, effective (e.g., mature) risk management teams must recognize when it is necessary to obtain input from experts when making quality management decisions and when building quality into investigational plan design.

Transparency is the mother of mitigation. Teams need support to get comfortable working through risks and issues across all functions and levels of an organization. Similarly, they need to collaborate proactively with outside stakeholder networks, working across vendors (e.g., CROs), and development partners. To be successful in utilizing Open Dialogue as an enabler, teams must leverage the diverse intellectual capital all around them, in a 360° manner. Access to the right data is important; however, it is equally integral to share the right data, right knowledge, and right information at the right time to the right audience.

Open Dialogue: Quality Partnership and Team Engagement

Open Dialogue is much more than just communicating in team settings; early discussions will need to include quality team members (e.g., risk and issue management)

to keep the flow of the discussion moving in the direction of “True North” where focus re-centers on trial participant protection and reliability of trial results. Quality stakeholders can help promote regular discussions around trial participant safety, data reliability, compliance risks and issues that may otherwise be de-prioritized. An authoritative or “policing” quality presence should be avoided in favor of transparency and partnership. Open lines of communication where study team members feel comfortable asking questions or highlighting concerns enable proactive quality engagement rather than teams waiting until an audit or inspection. Early collaboration in quality discussions enabled by impact analyses and an appropriate understanding of risk-proportionate data and processes is transformative when developing innovative mitigation strategies. During this process, the quality team must build mutual trust and maintain individual integrity during tough discussions, even with change-resistant team members. They must find equilibrium while challenging ideas, not individuals.

Team member engagement is fundamental to effective communication. How can you manage quality if team members are not engaged enough to proactively identify risks and to critically think of a proper control? Effective knowledge management strategies beyond team and 1:1 meetings should be considered when working to develop a high performing Culture of Quality inside an organization. Potential strategies such as podcasts, interactive polling, and pre-recorded messages coupled with breakout sessions and workshops are often effective to encourage meaningful engagement. Mature teams will have forums where individuals in diverse roles will regularly discuss quality matters and learn from one another. Examples of these forums may include:

- Communities of Practice designed to share examples of effective risk controls
- Lessons Learned sessions held after an audit, inspection, or management review of quality and compliance metrics
- Risk Strategy hubs to enable knowledge sharing, questions, concerns, and best practices

Since Open Dialogue is an important Culture of Quality Enabler, organizations must actively exchange data, information, and intelligence to enable Critical Thinking about how best to manage quality. However, organizations who have not mastered all or even some of these activities can still develop the attributes and practices necessary for a high performing Culture of Quality. In this case, a maturity model can be employed to determine an organization’s baseline and identify actions for strengthening the organization’s Culture of Quality.

Leveraging a Maturity Model to Strengthen Your Culture of Quality

Within the pharmaceutical industry, clinical development has often modeled best practices after Good Manufacturing Practice (GMP). For example, GMP colleagues have led the way by assessing Cultures of Quality and applying GMP rules-based QMS to the judgment-based environment of Good Clinical Practice (GCP). By the mid-2010s, the pharmaceutical GMP industry-leaders had deployed Culture of Quality assessment tools and maturity models, including the 2015 Parenteral Drug Association’s (PDA) Quality Culture Guided Assessment Tool [18] and the 2017 International Society for Pharmaceutical Engineering (ISPE) Cultural Excellence Report. [19]

To facilitate the translation of what a Culture of Quality means for clinical development in the current regulatory environment, we have created assessment tools/maturity models (hereafter maturity models) for the Culture of Quality Strategic Enablers. These maturity models use a self-assessment technique to determine a baseline for the components of the selected Strategic Enabler of current focus. This enables organizations to determine the actions necessary to advance to a higher level of quality performance for each enabler. Long-term, maturity models also provide benchmarking for growth and progress reporting (Fig. 3).

Critical Thinking: The Critical Thinking Cycle

Study teams face increasingly complex therapeutic areas involving biometrics, genomics, non-traditional study designs, dozens of vendors, disparate internal/external data sources, international site locations, and participant engagement strategies—all while seeking to work more efficiently and achieve a higher standard of quality. In the face of such headwinds, teams will often fall back on reactionary approaches to operational planning and robust quality management (e.g., good documentation, risk management, etc.) is forgotten until a quality issue or inspection arises. Even when teams are able to conduct risk assessments during the start-up phase, as soon as the data (scientific and quality) comes flooding in, team members become overwhelmed and distracted by an endless stream of urgent operational demands. Not surprisingly, proactive Critical Thinking skills tend to atrophy when firefighting becomes the normal way of working. Fortunately, Critical Thinking skills emerge when we strengthen our “mind muscles” using a systematic approach such as the 4 ‘A’s. The core components of this Critical Thinking methodology, the 4 As, are as follows:

Component	Deficient (Level 1)	Foundational (Level 2)	Advanced (Level 3)
Open Dialog	<p>Data Access and Exchange</p> <ul style="list-style-type: none"> ❑ It is onerous for team members to gain information. Data, information, and insights are not democratized. ❑ Processes are limited or made inefficient by system constraints; systems created without end-to-end user experience input. ❑ Knowledge management system is difficult to use (inconsistent content, ineffective data governance and taxonomy, low accountability for quality-controlled data being input into knowledge management system). ❑ No or low application of regulatory, inspection, and quality intelligence to clinical programs. ❑ Ineffective review, dissemination, and incorporation of lessons learned. 	<ul style="list-style-type: none"> ❑ Quality metrics consistently and systematically run across clinical, vendor and QMS data to holistically assess clinical enterprise state of control, process risks, and quality outcomes. ❑ Data governance and effective taxonomy enables QMS data lake (appropriate data ingestion, normalizing, linkage, analytics, reporting, and dashboards). ❑ Systems effectively enable quality processes. ❑ Knowledge management: lessons learned systematically cataloged in knowledge management system empowering training, process improvement, and future quality by design efforts. ❑ Efficient and effective sharing of information that enables timely reporting to health authorities. 	<ul style="list-style-type: none"> ❑ Holistic risk scoring, analytics, and dashboards (development compounds, processes, CROs, vendors, sites, regions). ❑ Teams engage in continuous data analysis; move away from only having descriptive analytics and towards predictive and prescriptive analytics. ❑ Creation of innovative metrics leveraging ML and AI to assure quality; move beyond “Was task performed?” to “Was adequate quality achieved?” ❑ Teams monitor the effectiveness of control strategies. ❑ Teams efficiently mine and apply regulatory, inspection, and quality intelligence to development projects and improvements. ❑ Data and information sharing with vendors, CROs, and development partners.
	<p>Leverage Diverse Intellectual Capital</p> <ul style="list-style-type: none"> ❑ Low or no QA/SME input requested by operational team during quality events, while managing recurrent non-compliance, or when addressing systemic risks. ❑ Downstream “fire fighting” or heroic efforts by team members in order to get “inspection ready.” 	<ul style="list-style-type: none"> ❑ When “gray area” quality events emerge, teams ensure needed expertise is present to fully understand context and make the best decisions. ❑ Presence of diverse partnerships leveraging the strengths of different perspectives, experiences, and functions (including CROs, vendors, and partnerships). ❑ Risk Strategy hub; staff positioned to leverage knowledge. 	<ul style="list-style-type: none"> ❑ QMS and QA framework agile enough to evolve with the changing landscape of participant needs, technology, therapeutic innovations, and regulatory requirements. ❑ Teams think beyond functions and even organizations. For instance, sharing quality intelligence across the industry with regulators, CROs, vendors, and partners.
	<p>Quality Partnership and Team Engagement</p> <ul style="list-style-type: none"> ❑ Risks and issues fully or partially hidden due to QA being viewed as the “Quality Police” ❑ QA not appropriately engaged when quality events arise during clinical development. ❑ Discussion(s) around trial participant safety, data reliability, compliance risks and issues are not occurring regularly (deprioritized). ❑ Reactive ways of working – outreach to QA only during inspections or escalations. ❑ QA’s level of impact is lessened due to delays in QA engagement and partial lack of transparency around a quality event. 	<ul style="list-style-type: none"> ❑ Achieving compliance by timely QA engagement during quality events (Serious Breach, right documentation practices). ❑ Quality discussion is prioritized at every team meeting (discussing quality is on top of each agenda). ❑ Teams aren’t afraid to ask questions about quality practices; they commit to respectful communication dynamics and to challenging others with respect. Master listening skills. ❑ Teams discuss opportunities for continuous improvement. 	<ul style="list-style-type: none"> ❑ Strong partnership with QA – quality professionals viewed as guides and partners who impart valuable knowledge. ❑ Open dialog and critical thinking behaviors embedded in activities supporting program or study, quality intelligence leveraged during QbD activities. ❑ Quality data, metrics, and analytics-driven team meetings focused on trial participant safety, data reliability, and compliance. ❑ Teams proactively work together to maintain a state of inspection readiness.

Figure 3 Culture of Quality Strategic Enablers, Open Dialogue Maturity Model.

- **Asking** questions proactively
- **Analyzing** the data related to those questions
- **Answering** the question
- **Acting** upon the answers

This Critical Thinking practice is action-oriented and should always end with meaningful activity focused on the priorities previously defined. Upon the completion of such action(s), the cycle should begin anew with questions to

explore new issues or follow-up on the effectiveness of prior actions. Through vigilance, new questions arise, and drive an examination to determine whether the current information available requires a refresh or expansion to answer the new question.

Critical Thinking in the clinical development arena must also ascertain if the information under review indicates that trial participant protection, reliability of trial results or compliance are now at risk. “Is our ‘True North’ affected?” is the first stop in quality Critical Thinking. To answer this question, teams must allow time for the Critical Thinking cycle to produce well-considered answers even if multiple cycles are required. In order to arrive at the best answers and next steps, the products of Open Dialogue must fuel the Critical Thinking cycle: data acquisition; input from competent subject experts; and effective discussion.

Leveraging a Maturity Model to Understand and Strengthen Your Culture of Quality and the Critical Thinking Strategic Enabler

Similar to the Open Dialogue Strategic Enabler, this maturity model is a self-evaluation tool that can determine an organization’s maturity baseline as well as identify the necessary actions to upskill Critical Thinking within the culture of an organization. During this evolution of culture, even with the support of Quality Enabler maturity models, there will naturally be a need for some degree of change management. Organizations may start as “Deficient” during self-assessment; however, this first baseline provides both an impetus for change and future encouragement to continue as it measures progress when viewed retrospectively. It is expected that functional organizations will have varying levels of maturity, competency, and capabilities but should all be collaborating to enhance its culture of quality (Fig. 4).

Following an initial assessment using the maturity model(s), deficiencies will need to be addressed and associated competencies developed prior to employing the Ask, Analyze, Answer, Act approach. Otherwise, management will need to be prepared to support teams and bridge identified gaps. Once established, as new information becomes available, there are further considerations and questions that can be generated to guide teams initiating the Critical Thinking cycle for the first time. Example questions are found in Appendix A. These questions are intended to provide support and inspire further inquiry but should not be used as an exhaustive list. Each of these questions requires deliberation, consideration, and time to obtain relevant information as per the Critical Thinking model. As teams work through these questions, they should have a curious mindset while staying focused on “True North” to avoid becoming overwhelmed by the data, details, or their own internal biases.

In the end, teams may also need to partner with quality and/or regulatory professionals to confirm the appropriateness of agreed action(s). Examples of potential actions are provided in Appendix B. It is important to note that while many of the example questions and actions seem relevant during the execution of investigational plans, most should first be applied during the creation of the investigational plan. QbD principles, ICH E6(R2)/Draft ICH E6(R3) clinical quality management frameworks, and the Culture of Quality Strategic Enablers are of greatest value before a clinical study or program begins.

Final Thoughts

The Culture of Quality Strategic Enablers brings to life the requirements in ICH E6(R2), *Draft* ICH E6(R3), and the clinical quality management system frameworks. Together, these Culture of Quality enablers Open Dialogue, Critical Thinking, Leadership Commitment, and Employee Ownership expand the Clinical Development Quality Management framework to support operational implementation. This gives clinical development teams a roadmap for cultural growth that will better safeguard trial participant protection, reliability of trial results, and quality compliance. Beyond clinical development, the Culture of Quality Strategic Enablers provides value for a variety of stakeholders spanning sponsor, services, and vendors within our industry. In the end, all contributors to a trial should work together to develop strategies that foster critical thinking and open proactive dialogue.

The more mature an organization’s Culture of Quality, the more agile its navigation of the ever-changing landscape of participant considerations, scientific breakthroughs, innovative therapeutics, and emerging regulatory requirements. Full adoption of these principles will pay dividends as sponsors rededicate resources to clinical trial execution rather than firefighting and re-work. Efficiencies and smarter resource deployment lead to expedited delivery of new therapeutics as well as a happier workforce. These benefits have become crucial to the future state of organizations such that individuals should not wait for leadership directives but instead take the initiative to begin exhibiting behaviors in line with these Strategic Enablers. The work should begin in earnest with the germination of a Culture of Quality at every level and function. We are all on a journey together and together we will reach our “True North.”

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Component	Deficient (Level 1)	Foundational (Level 2)	Advanced (Level 3)
Critical Thinking	<p>Ask</p> <ul style="list-style-type: none"> ❑ Checklist mindset - Teams primarily reviewing whether a task was performed or not, rather than questioning whether the task could be improved or create a higher quality outcome. ❑ Teams not engaged in proactive questioning, assessment, decision, and actions related to risk and issue management. ❑ Leadership is not engaged with teams to model inquisitive behavior and encourage questioning of status quo. ❑ Culture does not create a "safe space" for meaningful discussion and friendly debate. 	<ul style="list-style-type: none"> ❑ Teams consistently utilize a systematic risk and issue management framework to identify risks and issues, assess impact, conduct root cause analyses, and implement appropriate correction and prevention to ensure trial participant safety, data reliability, compliance, critical data, critical processes, and critical vendors. ❑ Teams ask questions and seek improvements related to: if urgent escalation, reporting, or intervention is needed; if process change or investigational plan updating is needed; if proper documentation is place to demonstrate achieved quality; if quality is being effectively measured; if adequate quality being achieved; if effective monitoring is in place? 	<ul style="list-style-type: none"> ❑ Teams retrospectively review whether good/bad outcomes were predictable and if not, evaluate why. ❑ Teams continually assess the fitness of risk thresholds unique to program data and processes. ❑ Teams use TMF quality metrics to predict process compliance and effective management of the QMS. ❑ Culture encourages individuals to question and challenge the status quo on a regular basis. ❑ Leadership actively engages team members by asking questions and encouraging individuals to behave in the same manner.
	<p>Analyze</p> <ul style="list-style-type: none"> ❑ Quality output metrics must be manually gathered; poor quality metrics system. ❑ No established process for collection and review of Lessons Learned. ❑ Teams are not effectively measuring quality for trial participant safety, data reliability, compliance, and critical data/processes. ❑ Knowledge is not captured, stored, indexed, or shared. No significant interaction with outside companies, or consortia. Inefficient data and information flow needed for effective assessments. ❑ Knowledge management system does not enable teams to leverage knowledge on their studies. 	<ul style="list-style-type: none"> ❑ Teams seek newly available information to determine if control strategies for original situation risks and issues are effective. Question whether further correction and preventive actions required? ❑ Teams employ a user-friendly interface to "mine" knowledge and apply it to their studies, programs, processes, systems, and vendors. ❑ Systematic methods used to capture situation, data, analytics, inspection, quality intelligence in knowledge management systems and processes to support future analyses. ❑ Succinctly and clearly explain how quality risks and issues were managed in a state of control and how quality was maintained during inspections (mock inspections, BIMO and equivalent checklists). ❑ Teams effectively leverage all available information and data from outside companies and consortia (DIA, Avoca, TransCelerate, SQA, Linking Leaders, GxP conferences, etc.). 	<ul style="list-style-type: none"> ❑ Teams leverage comprehensive metrics, predictive dashboards and risk scoring to enable efficient assessment of quality outcomes (not just whether a task was performed), management review and urgent action. ❑ Bi-directional flow of data and information between analyses and knowledge management system. ❑ Automated leveraging of industry-wide knowledge management resources (inspection, regulatory, quality intelligence; process, metrics, and benchmarks). ❑ Industry level sharing of risk and issue information related to sites, CROs, vendors, etc. ❑ Teams evaluate relationships between quality outcome metrics and identify deficient process, performance, or components in the investigational plan.
	<p>Answer</p> <ul style="list-style-type: none"> ❑ Teams are consistently unable to arrive at conclusions or make decisions about quality events and requirements. ❑ Teams make poor decisions due to immature critical thinking skills/culture or not adhering to open dialogue factors: data/info exchange, diverse intellectual capital, and QA/team engagement. 	<ul style="list-style-type: none"> ❑ Teams have regular forums for training and learning. ❑ Teams efficiently arrive at action-oriented conclusions and decisions. ❑ Teams ensure appropriate decision makers are engaged and right documentation is in place around quality events (decision, justification, implementation/effectiveness date, other ALCOA+ principles are followed). 	<ul style="list-style-type: none"> ❑ Learning organization where answers/conclusion/decisions are shared to drive awareness, understanding, and improved behaviors. ❑ Supports the development of team members and thought leaders inside/outside other companies. ❑ Teams promote thought leadership and solutions to process, system, and tool-related challenges. ❑ Executive leaders (e.g., VP and up) co-present (e.g., townhall and all-staff meetings) case studies on best risk and issue management practices.
	<p>Act</p> <ul style="list-style-type: none"> ❑ Teams miss required reporting windows related to trial participant safety, data reliability, and compliance. ❑ Teams react to escalated, process trends instead of proactively assessing process effectiveness. ❑ Teams consistently fail to escalate, report, intervene; and conduct proactive management reviews. 	<ul style="list-style-type: none"> ❑ With QA guidance, implement corrective & preventive actions. ❑ Transform data points into innovative and mitigating controls, update investigational plan, amend contractual terms with CROs, vendors, sites, and business partners. ❑ Expeditious-process agility – improve processes based on inspection observations and near misses, process risk metrics, and knowledge management tools. Manage process and organizational change, retire processes not creating value. Employ Lean Six Sigma to improve processes. Re-train appropriate parties. ❑ Ensure robust documentation (risk, issues, deviations, change, etc.). ❑ Conduct additional risk assessments including audits. 	<ul style="list-style-type: none"> ❑ Teams are proactively building innovative capabilities to assure quality (meta data, statistically inferred data/surrogate quality markers, enabling systems, risk scoring, and management review dashboards). ❑ Teams implement innovative and mitigating controls to manage enterprise risks and issues; pulling correction and prevention through sites, programs, processes, CROs, vendors, partners, and systems. ❑ Processes, systems, tools, and contracts are continuously updated with Quality intelligence.

Figure 4 Culture of Quality Strategic Enablers, Critical Thinking Maturity Model.

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Appendix A

Examples of Questions to Initiate the Critical Thinking Cycle.

- As I execute this investigational plan, does this new information affect trial participant safety, data reliability, or compliance?
- Does this information affect the ability to conclude the study?
- If the right data is not available to me, what surrogate data might help me critically evaluate this information?
- Given this information, is urgent escalation, reporting, or intervention needed?
- What is the root cause of the related risk or issue?
- Did the team know this quality event was going to happen – if not, why?
- What is the appropriate correction/remediation given this information?
- What risks will the team accept?
- For this situation, has the QMS been appropriately used?
- Has the team robustly documented (followed ALCOA+) this situation in the TMF?
- During an inspection, can I explain how I maintained a state of control while managing this risk or issue?
- Given this information, do I need to modify the control strategies or investigational plan?
- How will the effectiveness of the new control strategy be measured?
- What additional quality performance measures or monitoring do we need to protect trial participant safety, data reliability, or compliance?
- How does this information broadly affect the clinical enterprise including other programs, and enterprise-wide processes, systems, or vendors (impact assessment)?
- Is there a systemic issue that needs to be addressed?
- Is process change needed?

- Have I helped my organization learn from this information?

Appendix B

Examples of Potential High-level Actions in the Critical Thinking Cycle

- Report serious quality events (e.g., SB, recurrent non-compliance) to health authorities as appropriate.
- Urgently escalate the situation as appropriate (medical, data integrity department, management review, legal, etc.).
- Implement corrective and preventive actions.
- Transform data into innovative, mitigating controls that are proportional to the risks.
- Implement innovative, mitigating controls.
- Update the investigational plan to prevent future issues.
- Update contractual terms or governance documentation for CROs, vendors, or development partners.
- Retrain associated parties.
- Update related processes.
- Conduct additional risk assessments.
- Appropriately capture quality event information and remediation in knowledge management system to support learning and future improvement.

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