

Risk Based Quality Management (RBQM) - A Collaborative Approach to Holistic Clinical Trial Oversight

Authored by ACRO's CRO Forum's RBQM Working Group

Abstract

Developing, executing, and overseeing clinical trials is a complex process. Gaining reliable evidence from clinical trials is essential for appropriate decision-making activities regarding trial participants' safety and the reliability of trial results. As clinical trials have become more complex, the clinical trial process has faced significant operational challenges. As a result, sponsors must identify proactive ways to design quality into the study design rather than taking the reactionary approach of monitoring quality into clinical trials. Risk Based Quality Management (RBQM) rooted in Quality by Design (QbD) principals while applying Risk Based Monitoring (RBM) control mechanisms offers such a solution. This systems-wide approach encourages cross-functional engagement in a holistic and risk-based approach to clinical trial management and oversight. Ultimately it will be that framework which supports key decisions that will manage clinical trial complexity.

Problem Definition: Purpose & Need

The release of the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use E6 (R2) Good Clinical Practice guidance in 2016 emphasized that the sponsor should implement a quality management system utilizing a risk-based approach.¹ While the guidance provided core requirements, interpretation and implementation has varied greatly. Such variability in interpretations by sponsor and vendor organizations, such as Clinical Research Organizations (CROs) and technology solution companies, has resulted in a variety of sourcing models and approaches to Risk Based Quality Management (RBQM) system development and implementation.

ICH E6 (R2) Good Clinical Practice guidance recommends integrating risk-based approaches into a quality management system to:

- Identify, during protocol development, data and processes critical to ensure human subject protections, the reliability of trial results, and the risks to such critical data and processes;
- Evaluate the likelihood, detectability, and impact of such risks;
- Determine if risks are acceptable or if they must be reduced based on prespecified limits;
- Document and report risks in the clinical investigation;
- Review risk control measures periodically, to ascertain effectiveness of risk control measures and to take into account emerging knowledge and experience.¹

Effective RBQM implementation requires a strong collaboration between the sponsor and vendors that is based upon partnership alignment. No matter the size of the sponsor organization (e.g., large pharma, biotech), Risk Based Monitoring (RBM) and Quality by Design (QbD) principals should be rooted in a sound Quality Management System (QMS) framework to ensure human subject protection, product quality, clinical responsibility and reliability of trial results.

The goal of this paper is to share perspectives that will assist sponsor organizations in the creation of a RBQM system in partnership with their CROs and vendors. When a shared, proactive plan is established, sponsors and CROs/vendors can then tailor their oversight strategy to support improved quality and safety of clinical trial execution.

Historical Landscape & Objectives

Historically, to help ensure overall study quality including human subject protection and data integrity, the pharmaceutical industry has demonstrated sponsor oversight by visiting investigational sites at an established interval (e.g., every twelve weeks) and performing on-site monitoring with 100% source data verification (SDV). SDV was the primary mechanism to evaluate the integrity and reliability of the clinical trial data and subject safety.

In 2013, The Clinical Trials Transformation Initiative (CTTI) identified practices to increase the quality and efficiency of clinical trials by building Quality by Design (QbD) into clinical trials.² In 2019, the U.S.

Food and Drug Administration (FDA) in collaboration with European Medicines Agency (EMA) further supported this approach by stating “when good quality risk management and quality by design processes inform the development of RBM, effective implementation of RBM can maximize study quality by focusing monitoring activities on processes and procedures critical for the protection of trial participants and managing data integrity”.³ ICH E8 (R1) continues that “quality is a primary consideration in the design, planning, conduct and analysis of clinical studies and a necessary component of clinical development programmes.”⁴

ICH E6 (R2) supports RBQM by emphasizing that “the sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials; and the sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring alone.”¹ Therefore, a sound QMS must be established along with a protocol designed using QbD principals to build the foundation of RBM where the identified risks result in a tailored risk-based monitoring strategy to effectively utilize a combination of on-site and centralized monitoring as risk control mechanisms. This tailored approach utilizes the Critical to Quality (CtQ) data identified within the risk assessment to focus monitoring activities on what matters most. For example, on-site monitoring activities are focused on data only visible on-site using methods which bring greatest value (i.e. source data review (SDR)) while centralized data review is implemented when data is available off-site. An effective monitoring strategy makes most efficient and effective use of both monitoring activities.

While the industry agrees that RBQM is a best practice, implementation has not met industry expectations.⁵ A contributing factor has been the varied approaches to quality management and RBM implementation practices resulting in deficiencies and/or a duplication of efforts. Association of Clinical Research Organizations (ACRO) member companies support a proactive, collaborative agreement between sponsor and CRO/vendor to define the RBQM framework in support of effective and efficient clinical trial oversight.

Solution Details & Methodology

As stated within ICH E6 (R2), it is the sponsors’ responsibility to implement a system to manage quality throughout all stages of the trial process.¹ As TransCelerate introduced in 2016, an RBQM framework begins with a QMS grounded in corporate quality and strategic objectives⁶ (Figure 1). Although it is not a requirement for standard operating procedures (SOPs) to be present within each category, it is best practice to determine how each component fits within the wider RBQM framework. Within this framework, establishing the roles and responsibilities of the sponsor, both internally and externally should be well understood. Typically, agreements with details regarding operational execution across organizations are established and ways of working within these agreements are documented, or outsourcing manuals are developed, in order to consistently guide trial delivery. CROs and vendors have proven experience in flexible models which adapt and accommodate different sponsor strategies.

The following QMS components support the sponsor quality and strategic objectives and serve to demonstrate the sponsors’ oversight responsibilities to protect data quality and subject safety:

- Sourcing
- Knowledge Management
- Issue Management
- Documentation
- Roles and Responsibilities
- Technology
- Quality Metrics
- Policies/Procedures
- Risk Management

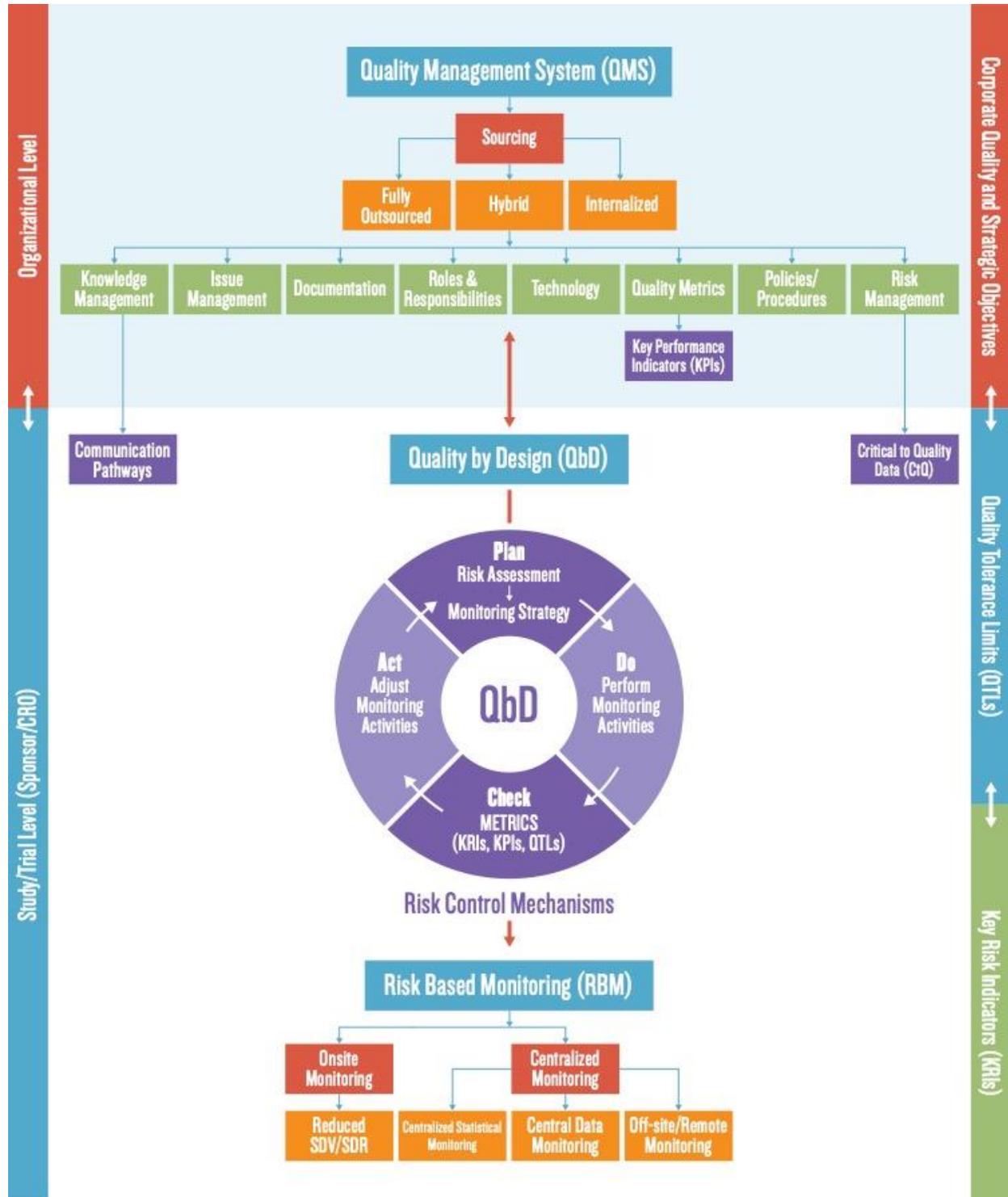
Sourcing Models

The first step a sponsor takes in establishing an RBQM framework is to identify the sourcing models that will be utilized. Sourcing can be broadly classified into three types, fully outsourced, internalized and hybrid:

1. **Fully outsourced** oversight is defined as a full-service, end-to-end solution with services typically provided by a CRO. The benefit of this approach is the utilization of complete CRO service offerings functioning under aligned CRO standard operating procedures (SOPs) to offer coordination while maintaining resource efficiency. This approach may be perceived as lacking “tight control” over outsourced partners and reduced procedural flexibility for modifications from the CRO’s defined SOPs, but it avoids handoffs between CRO and Sponsor at various stages.
2. **The internalized model** utilizes the internal staff of the sponsor and follows internal processes for maintenance of all trial activities. The benefit of this approach is clear and the sponsor has direct visibility into trial activities. This approach requires the sponsor to have complete systems, procedures and organizational structure in place to ensure adequate study delivery.
3. **A hybrid approach** includes components of both the outsourced and internalized models and is applied in a shared environment. This can also be viewed as a Functional Service Provider (FSP) relationship. Within a hybrid model, the sponsor may retain core responsibilities such as project management, while they outsource other services such as clinical monitoring or data management. Variations within this model can be seen when a sponsor collaborates in an alliance relationship across multiple CROs, with either a lead CRO or the sponsor retaining the project management responsibility. This approach may provide increased sponsor management activities but also may be complicated by the integration of multiple CRO/sponsor policies and procedures. Therefore, within a hybrid model, it is of greater importance to ensure that roles and responsibilities are well-defined and maintained as the processes to be used are new to both organizations or are a combination of both.

CROForum

Figure 1: Risk Based Quality Management (RBQM) conceptual framework in support of sponsor quality and strategic objectives.



QMS Components

Once the sourcing model is defined the QMS components should align in support of a holistic RBQM system. The following QMS components should be considered:

Knowledge Management

E8 (R1) highlights the importance that ongoing and future studies should be appropriately adjusted to take new knowledge into consideration and to protect study subjects and the design of the clinical study.⁴ It is important to consider how information will be shared across the partnership to ensure the state of knowledge. How are identified issues and supporting decision-making activities appropriately shared throughout the organization? Who will be responsible for sharing what information and at what time intervals? One method that can be used is to create escalation and communication pathways via an Integrated Quality Risk Management Plan (IQRMP)⁷ with associated functional plans (monitoring plan, data plans, communication plan, etc.) supporting the operational execution.

Risk Management

The process for risk management and the development of a risk-based protocol begins with the sponsor. The sponsor should begin by designing quality into a clinical study by identifying the critical to quality factors (CtQ) factors utilizing the historical state of knowledge and their experience with the drug and therapeutic area.⁴ These CtQ factors are attributes of a study whose integrity is fundamental to the protection of study subjects and the reliability of data collection.⁴ After the identification of CtQ factors, the risk assessment process occurs to identify and mitigate risks that have the greatest impact on subject safety, data quality and integrity, and regulatory compliance. At this point, it is important for the sponsor to determine the operational execution of the risk assessment process. For example, if the sponsor intends to utilize a hybrid or fully outsourced model, the determination of whether the sponsor's or CRO/vendor's SOPs will be used for risk management should be decided on and shared early on in a partnership agreement.

Issue Management

An effective issue management framework will improve identification, investigation/assessment, escalation and communication of significant issues

(i.e., "Issues that Matter").⁶ As TransCelerate identified, issues that matter materially impact any of the following:

- Patient safety, rights and well-being
- Data integrity and/or scientific rigor
- Compliance with regulatory requirements
- Trust in the clinical research enterprise

Identification and understanding of issues that matter and how they will be detected and who will be responsible for documentation and investigation should be well understood and established early in a partnership agreement.

Documentation

As information specific to CtQ data is generated and supporting actions and decisions regarding the interpretability of the study results, and overall oversight management are made, that information must be captured and stored. It should be determined where that information will be stored (e.g., eTMF) and who will be responsible for receiving and storing such information and at what frequencies.

Roles & Responsibilities

As noted earlier in the sourcing models section, depending upon which sourcing model is utilized the roles and responsibilities may be a blend between the sponsor and CRO/vendor. This makes the determination of what roles and responsibilities the sponsor will retain and which will be transferred to the CRO/vendor an important early step. This decision should be shared with the CRO/vendor as early as possible, preferably during the request for proposal (RFP) stage, to ensure an all-inclusive bid can be developed to ensure the proper roles and included.

Technology

With the growing importance of technology in the clinical trial development space, understanding what technologies are available and how they will be implemented is a decision which should be made by the sponsor early. Strong consideration should be taken to realize the impact of system integration prior to establishing an RBQM framework. This consideration should account for the assessment of system integrations to ensure that optimal knowledge and information sharing capabilities are established. This ensures that the correct data is available within the communication and reporting

pathways to enable and track data-driven and transparent decision making.

Quality Metrics

What is important is not knowing what the future will hold, but rather how to understand the data that is available at each point in time to make real time decisions; rather than predicting the future, you are reacting. A QbD approach includes a “check” component to monitor leading indicators of quality and ensure the defined risk control mechanisms are effective in mitigating the identified risks. These “check” components include such tools as Key Risk Indicators (KRIs) and Quality Tolerance Limits (QTLs). In addition to these “check” components at a study/trial level, quality metrics should be identified at the organizational level to ensure oversight mechanisms and actions remain effective at achieve the corporate quality and strategic objectives. This begins with the risk management processes and establishing appropriate performance thresholds such as Key Performance Indicators (KPIs) to measure the effectiveness of the monitoring strategy. E8 (R1) notes that “quality should rely on good design and its execution rather than overreliance on retrospective document checking, monitoring, auditing or inspection.”⁴ Therefore, quality metrics play an important role in sponsor oversight without placing addition unneeded constraints on CRO/vendors. These metrics should be developed early and fully communicated with the CRO/vendors in both hybrid and fully outsourced models to ensure that such metrics can be obtained and the intended outcomes achieved.

Policies/Procedures

Prior to entering a partnership agreement, the determination of whether sponsor or CRO/vendor policies and procedures will be used should be determined. This allows each party to communicate and design optimal clinical development strategies and ensures overlap and redundant processes are not created. In a hybrid or fully outsourced model this may be as simple as confirming that the sponsor will use the CRO/vendor processes, although those decisions should be made and understood as early as possible within an engagement.

Outcomes

Alignment of sponsors and CROs/vendors is key in order to follow a proactive structure to establish a collaborative partnership. ACRO’s members’ experiences have shown that independent of the sourcing model utilized, it is critical to align CRO management responsibilities with the sponsor’s QMS to reduce the risk of misaligned and/or duplicative efforts. In addition, alignment between sponsor and CRO/vendors ensures that the sponsors quality and strategic objectives are effectively shared back through the sponsor companies for application on future studies.

One outcome of a renewed focus on oversight and risk management is greater visibility into the risk management process and observations. A second outcome is the removal of emotional decisions in place of data driven decisions with supporting documentation regarding why and how those decisions were made. As CROs seek to remove barriers to meeting the needs of sponsors, there is a growing appreciation of the value of a collaborative oversight model. ACRO members support a proactive, collaborative agreement between sponsor and CRO to define the framework of oversight for the trial execution strategy. This framework supports the industry in taking the next steps in defining effective oversight strategies focused on delivering efficient RBM models.

About the Authors

The CRO Forum's RBQM Working Group members are subject matter experts in Risk Based Monitoring and Quality Management from ACRO member companies. The group comes together regularly to merge cross-company expertise from both CROs and technology solution companies.

We want to thank TransCelerate BioPharma Inc. and the Avoca Quality Consortium for their thoughtful contributions and input as we worked to develop this paper.

Further information on the CRO Forum and the participating companies involved in this effort can be found at acrohealth.org. You can reach to us directly at CROForum@acrohealth.org.

References

- ¹ International Council for Harmonization. 2016. Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)
www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Step_4_2016_1109.pdf
- ² Clinical Trials Transformation Initiative. 2011. CTTI Recommendations: Effective and Efficient Monitoring as a Component of Quality Assurance in the Conduct of Clinical Trials https://www.ctti-clinicaltrials.org/files/monitoring-recommendations_1.pdf
- ³ Duke Margolis, FDA. 2019. Improving the Implementation of Risk-Based Monitoring Approaches of Clinical Investigations [Video File]. <https://www.youtube.com/watch?v=xp8Wp0Upuvo>
- ⁴ International Council for Harmonization. 2019. General Considerations for Clinical Studies E8(R1) Draft Version
https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/E8-R1EWG_Step2_DraftGuideline_2019_0508.pdf
- ⁵ Ramsey, L. 2019. Risk-Based Monitoring Should Be Best Practice, ACRO Tells FDA
<https://www.centerwatch.com/cweekly/2019/05/20/risk-based-monitoring-should-be-best-practice-acro-tells-fda/> Accessed 26May2019
- ⁶ O'Connell, A.M., Sam, L.M., Bergamo, N., Little, J.A. Transcelerate's Clinical Quality Management System: From a Vision to a Conceptual Framework. Therap Innov Regul Sci J. 2016; 50 (4), pp. 397-413
- ⁷ TransCelerate BioPharma, Inc. 2016. Integrated Quality and Risk Management Plan (IQRMP)
<https://www.transceleratebiopharmainc.com/wp-content/uploads/2017/01/Integrated-Quality-Risk-Management-Plan-IQRMP.docx>