GUIDE

The Ultimate Guide to Risk-Based Quality Management (RBQM)

- An insider's perspective on RBQM's history and purpose
- Essential insights and simple strategies for implementation
- Proven best practices for more complicated applications

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Every organization faces unique challenges when it comes to implementing Risk-Based Quality Management (RBQM). There are numerous influencing factors, such as organization size and structure, therapeutic focus, and so on. At the same time, RBQM represents a set of universally applicable fundamental principles. **This guide explains these principles and provides an implementation framework along with proven best practices to ensure successful rollout and adoption of RBQM.**

The Evolution of RBQM

RBQM was encouraged by both the Food & Drug Administration (FDA) and the European Medicines Agency (EMA) through guidances published as early as 2011. It was more firmly incorporated as a GCP expectation in 2016 with the publication of ICH E6 (R2) and has been further reinforced with the publication of ICH E8 (R1) and ICH E6 (R3).

The motivation behind the significant shift in quality management is directly addressed in the introduction of the ICH E6 guideline, highlighting key factors from the past two decades. Firstly, there's the ongoing rise in complexity and cost of clinical research, evident in the increase in patient data, procedures, and trial durations. Secondly, there's the transition from paper-based to electronic methods like EDC, ePRO, and IRT. Research conducted by Tufts University clearly evidences this increasing complexity, as shown by the following statistics spanning from 2012 to 2020.[1]

- **68% increase in the number of procedures prescribed per patient**
- **69% increase in the number of participating countries per study**
- **27% increase in the number of endpoints being assessed**

This has been coupled with an exploding volume of patient data being collected per study, which will only escalate with the emergence of wearable technology for continuous patient monitoring.

A 2014 JAMA article analyzed NME submissions to the FDA from 2000 to 2012, revealing that 50% failed the initial review.[2] While slightly less than half of the failures were eventually approved for marketing, the average delay incurred was fourteen months. The most distressing of all is the possibility that up to 32% of all first-cycle failures—or up to 16% of all submissions—were due to issues with data quality.

A 2014 article, sponsored by TransCelerate, rigorously analyzed the impact of 100% source data verification (SDV) on data quality. SDV only impacted 1% of the eCRF data on average, while up to 15% of the total cost of research was driven by this traditional practice.[3] This highlighted the necessity for change in how we plan and manage clinical trials to ensure quality outcomes.

1. Getz K., Smith Z., Kravet M., Protocol Design and Performance Benchmarks by Phase and by Oncology and Rare Disease Subgroups, TIRS, 2023, 57:49-56.
2. JAMA, January 22/29, 2014, Volume 311: "Scientific and Regulatory Reasons for Delay and Denial of FDA Approval of Initial Applications for New Drugs, 2000-2012".
3. Therapeutic Innovation & Regulatory Science 2014, Vol. 48(6) 671-680 "Evaluating Source Data Verification as a Quality Control Measure in Clinical Research"

Understanding RBQM: A Simple Concept

What exactly is RBQM? As indicated, it's about "managing quality." Quality is paramount in clinical research, but let's review a definition of RBQM that encourages a shift to avoiding "errors that matter" rather than achieving no errors at all.

"Risk-based" is at the core of this approach. It doesn't suggest increased risk in clinical research planning and conduct; it's a method grounded in actively assessing and mitigating risk, which answers two fundamental questions: What could go wrong in our study? And how can we take action to reduce these risks?

> "Quality in clinical trials is defined as the absence of errors that matter to decision-making—that is, errors that have a meaningful impact on the safety of trial participants or the reliability of results."[4]

Risk assessment should be initiated as early as possible in the design phase, building quality into study protocol. Quality by Design (QbD) and Risk-Based Monitoring (RBM)—two concepts incorporated into ICH E8 (R1) and ICH E6 (R2 and R3)—can be understood as two phases of one RBQM paradigm, with both focused on improving operational success through risk assessment and mitigation.

QbD begins with research design, aligning with concepts like patient- and site-centricity to enhance research success by prioritizing relevant perspectives. It becomes RBM when a study protocol is finalized. At this point, risk assessment is repeated to ensure that all study logistics and quality oversight plans are focused on minimizing the opportunity for "errors that matter" to occur. This focus results in a refined quality oversight approach guided by centralized monitoring methods, which utilize advanced analytics to promptly identify and address pertinent issues with greater efficiency.

RBQM is straightforward; it's a framework centered on two principles: thinking before acting and focusing on what matters most. These principles elucidate the "why" behind RBQM, guarding against excessive process complexity, a common challenge in some implementations. To ensure sustainable success in transitioning to RBQM, start by defining your organization's primary objectives. Consider the three dimensions of RBQM value:

1. **Improved Quality:** Leading to more dependable stage-gate decisions and faster time to market.
2. **Reduced Operational Costs:** A more adaptive, targeted approach to site monitoring and data management reviews yields significant savings per study once RBQM is fully integrated.
3. **Shorter Timelines:** Achieved by enhancing enrollment and retention and streamlining the path to study database locks.

Additionally, establish quantitative success measures to periodically evaluate the impact of your RBM implementation on these objectives.

4. Clinical Trials Transformation Initiative (CTTI) Recommendations for Quality by Design.

Define Your RBQM Approach with Proven Best Practices

RBQM implementation can be overwhelming. Starting simple is one way to maintain focus and concentrate on the most critical elements. This principle is relevant not only during initial implementation but also as RBQM transitions into a standard, routine practice. A number of RBQM early adopters struggled to effectively move forward. One of the key factors conspiring against their success was a level of over-engineering that resulted in complexities. Implementation should be thoughtful yet pragmatic, avoiding unnecessary burdens. Pay close attention to specific areas such as pre-study risk assessment and mitigation planning, targeted SDV and source data review (SDR) plans, and the centralized monitoring approach for operational risk oversight. Here are some considerations for each of these critical areas.

Pre-Study Planning

A vital aspect of RBQM implementation is pre-study planning, which is most prone to over-engineering, posing challenges for busy clinical development teams striving to achieve the first-patient-in milestone. Rushing through this phase often results in superficial risk assessments, undermining its purpose. Addressing this challenge requires:

1. Appointing a dedicated champion to guide and coach study teams, especially during initial RBQM adoption. This individual should be well-versed in RBQM, passionate about its importance, and able to clearly communicate its value to the team.
2. Designing the process and tools for effectiveness, simplicity, and efficiency. A streamlined approach should require only a few hours of commitment from each team member. Avoid overwhelming teams with lengthy lists of predefined risk scenarios; instead, prompt them to identify potential challenges based on protocol categories, leveraging their expertise and critical-thinking skills.

Define Your RBQM Approach with Proven Best Practices

SDV/SDR Planning

While not critical initially, it's essential for your organization to progressively reduce reliance on SDV/SDR in RBQM implementation. SDV and SDR serve as one method, alongside centralized monitoring and other remote reviews, to ensure site compliance with GCP and protocol requirements. Initially, confirm compliance through source review of the first one or two patients per site. Once confidence is established and any issues addressed, limit ongoing SDV/SDR to periodic sampling, prioritizing critical patient data.

Avoid the temptation to assign varying levels of SDV/SDR based on predetermined site risk levels, as this overlooks their true role. Instead, initially, a consistent SDV/SDR plan should be applied to all sites, expanding only as needed to address specific risks or issues. This shift will allow site monitors to focus on key aspects during visits, foster better site relationships, and enhance patient recruitment and retention.

Central Monitoring

During study execution, effective centralized monitoring is pivotal for RBQM success. It comprises three key components:

1. Statistical Data Monitoring (SDM)
2. Key Risk Indicators (KRIs)
3. Quality Tolerance Limits (QTLs)

Quality outweighs quantity in central monitoring implementation, particularly concerning KRIs and QTLs. Avoid an excessive number of KRIs to prevent redundancy and false alarms. Instead, focus on optimizing a core set for early risk detection and minimizing false alerts. Similarly, prioritize essential study-level risks, or "failure points," for QTLs.

SDM, also known as Centralized Statistical Monitoring (CSM), is crucial yet often undervalued for effective quality oversight. Unlike KRIs and QTLs, which target pre-identified risks, SDM exposes various forms of study misconduct that may evade pre-study risk planning. By analyzing study data and audit trails, SDM detects atypical patterns indicating potential misconduct, including fraud, errors, training issues, and equipment malfunctions. Notably, statistical data monitoring identifies nearly 40% of confirmed issues in central monitoring, complementing KRIs' role in risk detection.

Organize for Success

Change management is another significant hurdle in successfully implementing RBQM, as with any significant process or technology initiative. Starting change management planning as early as possible is crucial, and while many of these considerations are no different from any other organizational change, they're worth repeating:

1. Secure full senior leadership buy-in and support. Without a clear, unified directive from the executive team, individuals may perceive failure as an option, leading to misaligned behaviors across the organization.
2. Identify RBQM champions and appropriate early adopters within the organization to generate successful initial use cases, fostering momentum. Use terms like "Early Adoption" instead of "RBQM Pilot" to convey confidence and avoid the connotation of potential failure.
3. Develop an RBQM training and communications plan, specifying stakeholders to be trained, training modules, timing, and communication channels.
4. Pay special attention to stakeholders likely to resist RBQM implementation, such as site monitors. Emphasize the strategic opportunities RBQM offers, reducing their focus on labor-intensive tasks like SDV. Address concerns from investigative sites with clear, reassuring communications.

Revolutionizing Your Approach to Clinical Research

RBQM is now an expected standard in GCP, offering your organization a prime opportunity for improved study quality, shorter timelines, and reduced development costs. Successful RBQM rollout hinges on simple yet thoughtful processes, strategic technology use, and effective change management. Complexity is not necessary for key RBQM components like pre-study risk planning, adaptive site monitoring, and centralized monitoring to be effective; in fact, simplicity enhances RBQM's impact. Embrace the principle of "focus on what matters most" as a guiding force in your RBQM implementation.

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