

## Establishing Risk-Based Monitoring within a Quality-Based System as “Best Practice” for Clinical Studies

### Introduction

The US Food and Drug Administration (FDA) requires that clinical trial sponsors “provide oversight to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality of the data submitted to FDA.” [US FDA 2019] This has traditionally been accomplished through onsite monitoring visits and 100% source data verification (SDV), in the belief that a comprehensive yet resource-intensive approach is the best way to achieve quality results. However, it has become clear that this type of approach is not only expensive and time consuming, it is also no guarantee of quality. As with an internet search algorithm designed to stratify results by relevance, optimal clinical trial monitoring requires an approach that focuses on critical needs rather than on peripheral issues unlikely to affect patient safety or data integrity. Regulatory authorities have recognized that this is best accomplished with a strategy known as risk-based monitoring (RBM), or the more holistic risk-based quality management (RBQM). This type of approach is now central to ensuring the safety of patients in clinical trials, and is expected to continue to grow in importance as clinical trials become more numerous and complex.

The US Food and Drug Administration (FDA) initially recommended use of RBM in 2013 [US FDA 2013], and in 2016 revised International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines established RBM as mandatory for all clinical trials [ICH 2016]. In 2019, the FDA followed up with additional guidance, reiterating the view that “risk-based monitoring is an important tool to allow sponsors to identify and address issues during the conduct of clinical investigations.” [US FDA 2019] However, RBM remains underutilized in clinical trials for reasons that will be outlined here. The importance of viewing RBM and quality-by-design (QbD) as part of a systems-based RBQM approach to clinical trial monitoring will also be discussed, as will recommendations for facilitating the uptake of RBM across the industry by leveraging the extensive expertise of contract research organizations (CROs) in this field.

### Defining the Terminology

As a starting point it is helpful to define essential terminology involved in clinical trial monitoring. Development of a protocol based on **quality-by-design (QbD)** principals provides an overarching trial-level quality approach to clinical trial oversight . QbD incorporates quality into clinical trial protocols at the initial design stage, helping to ensure that monitoring strategies prioritize factors crucial to patient safety and data integrity. [TransCelerate BioPharma 2017]. Serving as a foundation for quality control activities is **risk-based monitoring (RBM)**, “an adaptive approach to clinical trial monitoring that directs monitoring focus and activities to the evolving areas of greatest need which have the most potential to impact subject safety and data quality.” [TransCelerate BioPharma 2017].

The two primary components of RBM are onsite and centralized monitoring. **Onsite monitoring** includes a combination of **source data verification (SDV)** and **source data review (SDR)**. **SDV** is the basic fact-checking process of clinical trial monitoring, whereby case reports are cross checked against original sources to confirm the accuracy of the data and ensure the trial can be reproduced. [King 2015] **SDR** is distinct from SDV and does not involve checks against case report forms; rather, SDR includes steps such as reviewing source documentation and protocol compliance, ensuring that critical processes and source documentation are adequate, and assessing compliance with good clinical practice. [TransCelerate BioPharma 2017] The evolving availability of electronic data records has allowed for greater use of **centralized monitoring (CM)** where document review, data review and analysis can all be performed at a remote site, rather than sending inspectors to the investigator site. [EMA 2013] Taken together, a risk assessment supports QbD, and SDV, SDR, CM form key elements under what the FDA and EMA guidance reports have now acknowledged as the holistic approach of **risk-based quality management (RBQM)**. [EMA 2013; US FDA 2019]

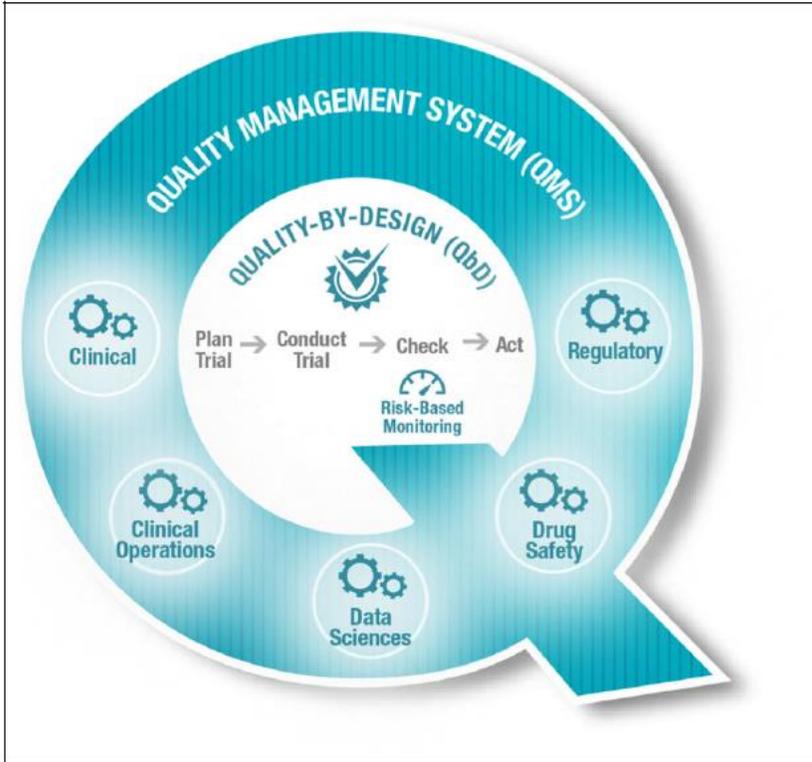
## A Deeper Look at RBQM

At an FDA workshop in July 2019, David Burrow, Director of the Office of Scientific Investigations in the FDA's Center for Drug Evaluation and Research, noted that in today's clinical trial environment the FDA strongly encourages approaches to clinical trial monitoring that place quality front and center. In this context, it is more appropriate to consider RBM as one facet of a quality-based system designed to produce "an absence of errors that matter." This is a distinction of importance because all stakeholders in the clinical trial process have a shared interest in the development of safe and effective therapeutic agents while maintaining confidence in the clinical trial process. [US FDA 2019]

Unfortunately, some view RBM as an end in itself rather than as a tool within a holistic quality-based system, and in some cases may simply attempt to fit an RBM strategy on top of an already developed protocol. Such an approach is unlikely to be successful, and often adds unnecessary cost. To fully implement RBQM, the FDA has laid out three necessary steps to be taken in sequence. [US FDA 2019] First, a risk assessment must be conducted both pre-study and ongoing during the trial. Second, a well-articulated study protocol should be developed based on factors identified during this risk assessment. Finally, an RBM approach can be tailored based on both the risk assessment and study protocol.

Importantly, this move towards RBQM is not only a regulatory priority in the US but also globally. The EMA has for many years encouraged greater adoption of quality measures to improve clinical trial monitoring. [EMA 2013] In 2013 the EMA published guidelines that support the FDA's current emphasis on situating clinical trial monitoring within a quality-based system (a general view of RBM and QbD within a quality management system can be seen in **Figure 1**). Of particular note, the EMA is aligned with the FDA guidance on a sequential process for RBQM, stating that the identification of risks in a clinical trial "should start at the time of protocol design so mitigation can be built into the protocol and other trial related documents (e.g. monitoring plan)." [EMA 2013]

**Figure 1. Relationships across quality management systems, QbD and RBM**



Meeker-O’Connell A et al. Ther Innov Regul Sci. 2016;50:397-413. .

### **Real Benefits Have Already Been Achieved with RBM**

It should be emphasized that RBM is not a new idea in the field of clinical trial monitoring. The tools and strategic aims of RBM have long been in place in other industries such as banking and aviation, and RBM itself has been a component of the clinical trial space for over a decade. As a point of comparison, RBM methodologies were incorporated into only 18% of new clinical trials in 2016, but that number rose to 41% in 2017 and 61% by 2018. [ACRO data on file] An important caveat to this finding is that definitions of RBM vary among organization, making it difficult to fully define the prevalence of RBM in clinical trials, nor does it address the issue of whether the RBM approach was appropriately implemented in a quality-based system. Nevertheless, the weight of evidence points to the growing importance of RBM in clinical trial monitoring.

## ***CROs Have Developed Extensive Expertise in RBM.***

*Association of Clinical Research Organization (ACRO) member companies are positioning RBM at the heart of their mission to help bring efficiency, innovation and value to the clinical research process. A recent survey by ACRO found that all companies now include RBM as the default choice for monitoring in their contract bids. In addition, CROs have expanded their workforces over the past 3-5 years to support increased use of RBM in clinical trials, and have updated the training procedures for this new workforce, including courses on risk assessment, corrective/preventive actions, and use of data analytics software. CROs are also investing in new RBM-centric technologies, such as software applications for centralized monitoring, risk assessment and planning tools, and data analytics and visualization platforms. [ACRO data on file]*

CROs have increasingly incorporated RBM into clinical trial monitoring not only in response to FDA and global regulatory guidelines, but also because they have seen firsthand how RBM and QbD strategies, when appropriately integrated into a systems-based approach, provide direct benefits to sponsor companies and improve the quality of clinical trial data. In 2019, ACRO surveyed its members about RBM metrics related to quality, efficacy and speed [ACRO data on file] [Table 1]. With respect to quality, this survey found, among other things, that when a company reviews data through a centralized system, investigators are better able to detect quality issues earlier and make rapid corrections. For example, one company reported a 16% reduction in critical and major findings in site audits, and a 17% better detection of significant deviations were also reported with RBM. With respect to quality and efficacy, a large sponsor reported a 10-day reduction in data management cycle time, while a smaller biotech reported that database locks from last patient visit decreased from 30-60 days to about 5 days. Similarly positive results were found in an analysis by Agrafiotis and colleagues, who looked at 4 years of data from RBM studies incorporating QbD, CM and triggered, adaptive on-site and remote monitoring. [Agrafiotis 2018] They found that RBM significantly improved clinical trial monitoring while also reducing costs, including 28% fewer critical and major findings per clinical quality control visit and a 16% lower mean cost per monitoring visit.

## ***Leveraging the Expertise of CROs: The Stories Beyond the Numbers.***

*Many ACRO members report success stories that have furthered their commitment to RBM. In one study of epilepsy, for example, inappropriate tapering of treatment was prospectively identified as a risk factor requiring a more focused level of monitoring with an RBM approach. Using CM rather than more time-consuming onsite monitoring and SDV, the CRO was able to rapidly identify patterns in dosage tapering across clinical sites and immediately alert principal investigators about potential risks to patients who were not tapering the drug according to protocol.*

It may seem counter-intuitive that RBM, which is less time consuming and resource intensive than 100% SDV and onsite verification, could provide higher quality. It has now become

evident, however, that SDV does not equal quality. For example, TransCelerate, a non-profit organization comprised of pharmaceutical and biotechnology companies working to simplify and accelerate clinical research, conducted a retrospective analysis of monitoring and SDV conducted by 6 member companies. This analysis found that, of all the SDV queries generated during the monitoring process, only 2.4% related to data that was considered critical for ensuring quality in the clinical trial. [TransCelerate position paper 2013] Another study examined 268 findings from on-site monitoring and found that 28% of them could have been identified in the study databases, while another 67% could have been identified with central checks such as review of back-translated documents. Overall, only 5% of findings required onsite monitoring, and these findings were all minor. [Bakobaki 2012]

**Table 1. Examples of RBM trial evaluation metrics reported by ACRO survey respondents [ACRO data on file]**

<b>Quality in RBM Trials</b>	<b>Efficiency and Speed in RBM Trials</b>
Enhanced ability to identify and manage patient eligibility issues, unreported adverse events and protocol deviations, helping to monitor safety risks	10-day reduction in data management cycle time for a large sponsor implementing a new RBM technology
Central data reviews enabled early detection of quality issues, allowing sites to identify data issues and make early corrections	A smaller biotech has seen database locks go from 30-60 days from Last Patient Visit (LPV) to about 5 days
16% reduction in critical and major findings in site audits	40% faster database lock timeline compared to non-RBM trials
17% better detection of significant deviations	20% reduction in SDV, resulting in more than \$1M savings for a mid-sized sponsor in the first year
4x lower error rate in critical data in a head-to-head comparison of RBM to traditional 100% SDV approach	3-15% savings over traditional monitoring, depending upon the level of SDR/SDV included
45% reduction in the number of missing pages in RBM trials versus traditional trials	21% reduction in subject visit data entry lag

### **Underutilization of RBM in Clinical Trials**

Given the benefits of RBM for improving the clinical oversight process while also reducing costs and use of resources, why is RBM still underutilized in clinical trials? In the 2019 ACRO survey

noted previously, member companies reported multiple challenges that may limit wider adoption of RBM centering on perception and expectation management (**Table 2**). [ACRO data on file] For example, some companies reported misperceptions that traditional monitoring methods are lower risk, that the strategy of checking every data point is safer, and that complete SDV is the best way of ensuring data quality. In a survey of 132 academic clinical researchers, Hurley and colleagues found that many of the perceived barriers to RBM implementation stemmed from lack of knowledge of the process, including misperceptions about cost benefits and lack of knowledge about evidence supporting the use of RBM. [Hurley 2017]. Among the responders in this survey who categorized barriers to CM, the most common reasons cited as “very important” were lack of education and training in CM (62%) and information technology demands associated with CM (46%).

The 2019 ACRO survey also found that “change management” was a significant challenge in facilitating the uptake of RBM. [ACRO data on file] This may be due part to the sheer number of stakeholders involved in RBM, ranging from CROs to sponsors to research sites, all of whom must commit to moving away from “tried and true” methods for clinical trial monitoring. Moreover, these multiple stakeholders represent only a portion of the machinery necessary for RBM to run efficiently. Other gears that must fit together seamlessly include specific components of RBM such as initial risk identification, as well as broader components of a quality management system such as data sciences and clinical operations (**Figure 1**). Moreover, all these gears must work in a way that provide cost efficiency. For example, adding CM to clinical trials can improve patient safety, but if at the same time 100% SDV is kept in place, costs can actually increase. In addition, as noted previously, optimal RBM requires a sequential order of operations that starts with a foundation of appropriate risk assessment followed by development of well-articulated study protocols.

Another challenge has been not only to integrate all of the steps of RBM within a quality-based system, but also establishing a “chain of custody” for clinical trial data among the multiple stakeholders. For example, in some cases the sponsor may be responsible for electronic data capture, the CRO for data management, and another party for centralized monitoring, leading to a situation where data and data sources are not centrally maintained and accessible to all parties. With all of these moving parts, it is not surprising that some companies are reluctant to turn away from traditional strategies for clinical trial monitoring.

**Table 2. Challenges limiting the wider adoption of RBM reported by ACRO survey respondents [ACRO data on file]**

Perception Management	Expectation Management
When sponsors request 100% SDV, it is often due to their comfort level with traditional oversight methods and the perception that 100% SDV is the only way to ensure data quality, and thus a “lower risk” market application	Non-directive guidance creates varied performance expectations regarding RBM implementation (eg, reduced SDV/source data review) by sponsors, CROs and research sites

Emerging biopharmaceutical companies with limited portfolios tend to be the most reluctant, choosing what they see as a “safer” strategy of “checking” every data point	Varied interpretations of ICH E6 (R2) requirements relating to RBM and quality tolerance limits, creates variability in inspection findings
Sponsors perceive audit and inspection findings at research sites, with findings for non-critical discrepancies, as further support for 100% SDV	Variability in inspection findings creates variability in stakeholder incentives – positive and negative – to implement RBM
Sponsors may also request RBM initially, but then identify additional data points as critical, resulting in little reduction in SDV.	RBM implementation requires consistent and ongoing investment in change management by all parties, including regulators, sponsors, CROs and investigative sites

## Facilitating the Uptake of RBM

Although RBM has become a more common element in clinical trials over the past few years, it is the position of ACRO that it continues to be underutilized. To encourage more widespread implementation of RBM, ACRO recommends that it be accorded the status of “best practice” by the FDA. In the survey conducted by Hurley and colleagues noted previously, 58% of respondents who used RBM reported that they did so to meet regulatory requirements, suggesting that a stronger emphasis on regulatory-endorsed guidelines could potentially broaden the uptake of RBM. [Hurley 2017]

Other potential facilitators noted by Hurley and colleagues include additional training for investigators to better understand the benefits of RBM, including potential financial advantages. [Hurley 2017] However, improved education about RBM may be insufficient for companies and investigators that lack the time and resources to navigate the complexity of clinical trial monitoring. RBM in and of itself is simply a risk-mitigation mechanism that needs to be situated within a holistic systems-based approach to clinical trial monitoring. Rather than focusing on specific segments of RBM such as reduced SDV and on-site monitoring, CROs can help sponsor companies incorporate the concept of “data knowledge” (or all of the knowledge the company has about the drug) into a systems-based approach that aligns with the sponsor’s strategic objectives.

CROs with extensive experience in clinical trial monitoring are ideally suited for guiding sponsors through this process, helping to adjust the multiple gears of RBM into a “finely calibrated machine” that optimizes data integrity and patient safety. While it may seem tempting to “pick and choose” just a few of these different gears for a given clinical trial, such a piecemeal approach runs the risk of increasing costs (by not removing unnecessary steps) or decreasing quality (by not adding critical steps). CROs can work with sponsors to compile a checklist of the most important elements of RBM and advise on how to consistently integrate these elements into a quality-based system. It should be emphasized that cost savings may not emerge immediately with RBM; this can be achieved as larger efficiencies are created through broader adoption of RBM methodologies.

To improve strategic decisions about outsourcing elements of a clinical trial, it is also recommended that sponsors collaborate with CROs as early as possible in the process to establish a chain of custody for clinical trial data. This collaboration should begin early in the trial planning process when outsourcing decisions are made so that all parties understand where data needed for centralized monitoring will reside and who will have access to the data (including e-diaries, electronic data capture, imaging results, etc).

Finally, implementation of RBM across the industry will require acceptance of change and creation of new roles in clinical trial monitoring, such as risk managers and central monitors who possess both clinical and data analytic skills. Integration of older and new technologies will also be critical, for example, by developing strategies to incorporate data gathered by CM into older clinical trial management systems so that it is readily usable by clinical research associates.

## **Conclusions**

RBM is central to clinical trial monitoring, with the FDA and international regulatory agencies increasingly encouraging its use as part of a quality-based system, or RBQM. A growing body of evidence shows that RBQM represents a best practice for identifying issues during clinical trials, and RBM as a method to mitigate identified risks is in fact an approach that other industries have already used for years. However, even after more than 5 years of regulatory guidance, there is some reluctance by sponsors to fully embrace RBM, in some measure because of the natural fear of change, and in other measures because of the complexity of implementing a systems-based approach for clinical trial monitoring. While some of the challenges in implementing RBM are daunting, they are by no means insurmountable. CROs have vast experience in RBQM and RBM implementation and are uniquely positioned to partner with sponsors through the risk assessment and monitoring activities to ensure subject safety and data quality throughout the lifecycle of a clinical trial.

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