WHITE PAPER

IQVIA TECHNOLOGIES

Right Sized RBM Solution For Your Trials

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Introduction

Risk-based Monitoring (RBM) has been evolving into a mainstream choice for the critical monitoring aspect of clinical trials.

This paper is actually the first in a short series of two papers written by the same authors taking you through:

1) Implementing RBM from an Operational Standpoint – your journey through the early stages of RBM, critical decisions to be made in identifying the right approach for your particular needs, de-risking your protocol, centralized monitoring, and more.

2) Implementing RBM from a Technological Standpoint – and on to implementation challenges and lessons learned, including data integration, automation of processes using AI and machine learning (AI/ML) with advanced and predictive analytics.

We appreciate your interest in RBM and invite you to reach out to us at any time. We have a long history of providing strong value to our customers by using RBM and we're happy to share our experiences with you!

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Background and getting to today

The move to RBM was initially fueled by the **International Council for Harmonisation (ICH) E6 – Good Clinical Practice (GCP) guideline,**[1] requesting sponsors to maintain greater trial oversight and use a more formal approach to quality management, combining new technology and timely data.

While the ICH's 2016 Guidelines encouraged companies to adopt RBM as a strategy and to focus more on formalized quality management and timely data, many companies are uncertain about how to execute the requirements.

There are still many unknowns within RBM, and while guidelines have been provided, strategies for creating an effective risk plan have not been established that provide clarity on how companies should specifically undertake the task of creating a study risk plan, identifying critical protocol data and key risk indicators to monitor site performance. At this stage, many companies simply do not have the technology and experience to effectively implement RBM requirements, including creation of new workflows backed by technology, and integration of multiple data sources.

This initial uncertainty increases with additional technology needs: SaaS tools for remote monitoring; the ever-present buzzwords of artificial intelligence (AI) and machine learning (ML); advanced and predictive analytics.

Nevertheless, it is vital to understand these innovations for effective implementation of RBM to:

- **Fully integrate trial data** for a single, transparent source of truth across groups
- **Create efficient data ingestion pipelines** to better understand the risk landscape in near-real time
- **Construct a robust analytics suite** providing multiple perspectives to critical operational and trial, site, and subject-level risk metrics

There are companies that can facilitate the introduction and implementation of RBM leveraging their experience, expertise and innovative technologies. This can ease the transition to RBM despite any trial complexities. The first step is simple:

- **Understand the available options** for RBM adoption
- I**dentify a trusted partner with RBM expertise, such as IQVIA,** to oversee the entire process, or to buy a product with the necessary technologies and train staff in RBM requirements

[1] https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

An early decision that a company would make when integrating RBM customs and technology is either to own and control all of the RBM processes themselves, or to leverage a third-party expert such as a CRO to run some or all of the RBM processes. Each choice comes with its own advantages. There are a number of elements that must be considered during implementation:

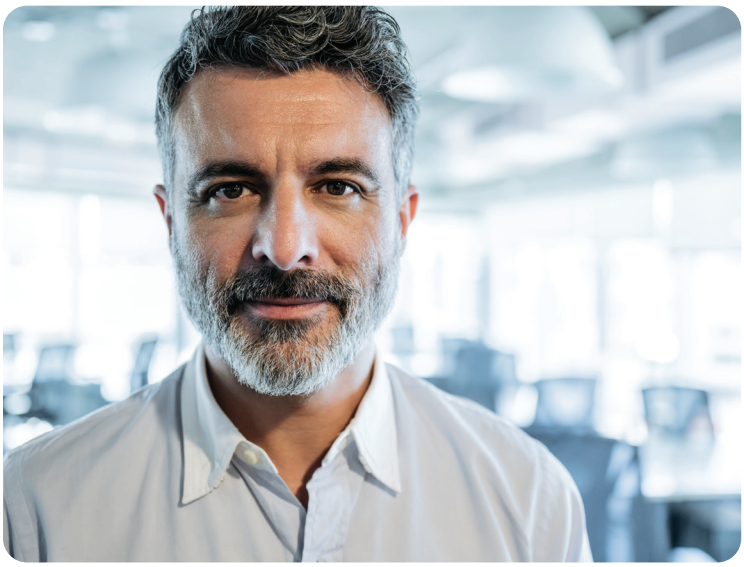
- **Whether the project scope aligns with the end user's needs,** and that all roles and responsibilities are clearly defined
- **Whether current plans and procedures** are either fit-for-purpose as-is, or can be updated to fit within the new model, or whether new processes must be created around the RBM implementation
- **How success and added value will be measured and communicated** to stakeholders
- **How communication to both technology vendor and consumer** will be organized and managed
- **Which resource gaps or knowledge gaps currently exist** in the organization and what resources could be leveraged to reduce these

Clearly, hiring an organization such as IQVIA is enormously beneficial to a company just entering the RBM space. The full experience and expertise of the CRO can be leveraged in the setup and operation of RBM. This means less trial-by-error, fewer costly mistakes, and no time lost in training staff that could be employed elsewhere.

However, there is also great value in a company owning the RBM technology entirely and in having greater oversight of the trial conduct than might otherwise be the case. It is important to note that, when a company chooses to own the RBM technology built by IQVIA, it could leverage technology and advisory support from IQVIA to move to the RBM model, and ensure the requisite processes are in place once the technology set-up is completed.

For those wishing to simply buy the technology and take ownership, IQVIA can provide full staff training in RBM, as well provide support to perform the necessary tasks and processes. With this in-depth consultation, companies can establish optimal resources, ensure their data is centralized and reviewable, while still controlling oversight of the processes. The right solution depends entirely on the individual company needs and their level of comfort in investing in an RBM solution.

From here, RBM improvements fall into two wide categories: **operational and technological**. Fortunately, IQVIA can support both requirements.



Implementing RBM from an operational standpoint

De-risking the protocol

The ICH Guidelines recommended replacing the current pharma focus on total data accuracy with one of protecting key outcome data from risk. To shift this focus, the ICH set out four requirements to improve company risk assessment as a crucial part of trial monitoring:

- **Critical protocol process** and data identification
- **Risk identification** at program and trial level
- **Evaluation of risk by ability** to review data, impact and extent of occurrence
- **A 'systematic, prioritized,** risk-based approach to monitoring'

De-risking begins at the initial stages of a study, often at the compound level. Here, it is easiest to understand certain aspects of the product (e.g., the research associated with it, potential side effects and risks from the compound alone) and begin to build a more concrete risk assessment that can then be applied at trial level. It is essential to carry out this assessment in the protocol development stage, as risks may increase with delay in performing this assessment. However, if for some reason de-risking is not performed at the initial stages of a study, it would provide value by performing this assessment at a later stage to ensure compliance with the ICH Guidelines and thereby reduce the overall study risks.

A key part of this new focus on de-risking is in consolidated regulatory documentation. According to the **FDA's Guidance for Industry: Oversight of Clinical Investigations – A Risk-based Approach to Monitoring**[2] while flawless data is not key, what is expected is clarity around identifying trial and protocol risks, how risks are measured, risk tracking and mitigation ownership; specific trial endpoints; identification and maintenance of subject safety and ensuring informed consent has been obtained.

Creating a cross-functional perspective and collaboration within an organization is vital for optimal de-risking. Traditionally, the role of monitoring fell largely on the CRA as the individual performing 100% source data verification (SDV) at sites, but with decentralization and the need for a more holistic examination of risk in clinical trials, it must now be expanded to encompass a number of roles within a pharma company.

This wider range of stakeholders brings in several unique and vital knowledge bases that together comprise more than their individual parts. Statisticians can speak to the need for certain target populations and how a trial will be affected by patient drop-out or delayed enrollment; safety managers should justify selective safety reporting processes in the protocol. Other experts whose knowledge could benefit the monitoring process include biostatisticians, medics, data processing personnel, and technology support experts, in addition to the clinical team.

[2] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/oversight- clinical-investigations-risk-based-approach-monitoring

The ability to highlight trends that one individual expert with one background may not identify, is enormously important to overall risk management and a more rigorous approach to monitoring.

Nevertheless, it is still important to train key individuals in risk assessment who can drive the entire process and oversee risk across several individual trials and/or therapeutic areas.

These individuals could come from any number of backgrounds, and ideally must:

- **Have strong knowledge of the protocol,** including the study's methodology and objectives
- **Be able to interact with and understand individuals** from a wide range of backgrounds and functions, and have a strong clinical knowledge foundation to understand why issues are raised and under what circumstances
- **Work continually with risk assessment goals** and understand them thoroughly, including knowing the difference between critical and non-critical issues, and prioritizing them effectively

Centralized monitoring

100% SDV contributes to a significant portion of clinical trial costs. Traditionally, while not regulatorily required, SDV has been considered a necessity to ensure high data quality. That idea has increasingly been regarded with suspicion: since in 2014 studies found 100% SDV practices lead to only 2.4% of site-entered clinical data being corrected3 across all data: the true value and efficiency of SDV has seemed increasingly limited.

Where SDV has failed, centralized monitoring (CM) has succeeded. The benefits of monitoring protocol-related data centrally are numerous, most evidently with regards to subject safety and eligibility due to the ability to review data in near real-time, and the quality of data versus the latencies inherent to site visit oversight. Other improvements include benefits to site visit oversight and its ability to create efficiencies in on-site monitoring, to better identify data fabrication and any critical data that could affect safety or efficacy. It allows sponsors to determine sites with increased risks and prioritize monitoring processes critical to trial success.

Due to these capabilities, CM naturally leads to cost and resource reduction in trials, through efficiencies created by reducing site visits and duplications of work and effort as a whole.

[3] https://www.transceleratebiopharmainc.com/wp-content/uploads/2016/01/TransCelerate- RBM-Position-Paper-FINAL-30MAY2013.pdf

Many companies have already found value in this move towards RBM: reduction in clinical development costs from fewer on-site visits; higher study data quality leading to higher marketing approval rates; reduced timelines through better monitoring of data at the study, subject and site performance levels.

When the choice to commit to CM has been made, there are several further factors to consider for implementation. First and foremost, it is vital to identify the critical data within the protocol and to know which data can be reviewed centrally, as data critical to the endpoint analysis must be available to review remotely. It is key not only to have a central monitor review the data for incongruencies, but also to review the data/ analytics on a fixed cadence (ex: monthly) to identify current trends and issues.

This is obviously impacted by any reduction in data. For instance, a slowdown in enrollment rate would reduce relevant data availability. The duration or complexity of a trial, or the number of vendors involved, can also impact analysis and integration. Nevertheless, ensuring at least the bulk of available data is centrally available for review will allow the centralized monitoring team to gain valuable insights pertaining to the near real-time risk landscape.

There are many other variables to consider when implementing CM in (particularly smaller) trials:

- **Ensure the monitoring strategy is aligned with the outsourcing strategy**. The on-site and centralized monitoring effort must be harmonized to ensure these functions are working together on issue escalation and risk mitigation
- **Tracking and management of issues, protocol deviations and safety events** provides the study team with the means to resolve issues in a coordinated fashion, deploying best practices across the studies as the team is given a transparent view of all issues and mitigation strategy actions across the study
- **Site staff working with centralized monitoring teams** – It is important to gain the buy-in from your participating investigators and sites to ensure a productive working relationship with the centralized monitoring team

Orchestrated applications can solve these problems in the simplest and most efficient manner. These applications are horizontal by design, and harmonize analytics, new technology and best practices into a system that can capture both active and passive signals from multiple stakeholders before sharing insights among the study team. Such systems ensure there is only one source of truth and complete transparency across all products, personnel, and customer groups. They also paint a nearer-to-real-term risk landscape, as they bring in data from multiple sources with less latency and can run advanced analytics and reporting tools to help teams make better and more informed decisions.

By looking at data in real-time with the integrations and visualizations that are currently available, issues that would otherwise have been seen too late can now be identified and prevented. This, in turn, allows more study data to be captured as per protocol, leading to more congruent and subsequently valuable data during the end-point analysis.

Companies such as IQVIA have an enormous amount of experience in RBM, starting from the identification of critical data/processes and key risk indicators that should most closely be tracked, to the technology for identifying risks and trends, to data analysis, and the metrics vital for reviewing site performance. Leveraging IQVIA's experience and dedication to the area also means that process enhancements and updates can be carried out swiftly, pushing a company's RBM operations ahead of the curve.

The operational RBM expertise is integrated into every aspect of IQVIA's RBM product. Given IQVIA's long-established, exceptional track record working with RBM, the company's experts have percolated their knowledge into their technology. For example, IQVIA's experience in identifying key Critical Data/Processes (CD/Ps) and Key Risk Indicators (KRIs) at trial and therapeutic area and indication levels has been leveraged to facilitate automated risk plan creation, where risk plans have been templatized at the therapeutic area to ensure quicker study risk plan creation, building greater efficiencies into the process. These features and others such as automated action item creation and assignment of alerts and action items to specific roles and personas are incorporated into IQVIA's RBM technology, owing to their incomparable experience in the field.

When transitioning into the RBM space, **selecting the right technologies is vital.** It is important that no half-measures are taken: buyers should ensure their new systems fully assess trial risks, working to identify and manage risks with regard to both context and further analysis. Among other things, it is vital that RBM technologies:

- **Allow users to assess and characterize risks** at start-up and throughout the trial's lifecycle
- **Have risk management strategies** to control and mitigate identified risks
- **Have models and visualizations** to allow a centralized review of risks detected
- **Predict risks** without singularly relying on historic or retrospective data for insight

Sponsor benefit from RBM technology solutions

The technological means to integrate RBM into general company processes can seem daunting to those new to the area. Ultimately, however, much of this technology is geared towards simplicity and streamlined user interfaces (UIs), and is backed up by the RBM vendor's significant expertise using these products. Furthermore, the technologies available today often cover almost every necessary aspect of RBM, from early assessments to endpoint monitoring.

IQVIA's RBM solution, for example, is geared towards flexibility, focusing on the three key elements of RBM: **risk assessment, data surveillance, and dynamic monitoring.** IQVIA works with sponsors to jointly conduct trial risk assessment, identifying all protocol-critical variables and the optimal monitoring strategy as swiftly as possible.

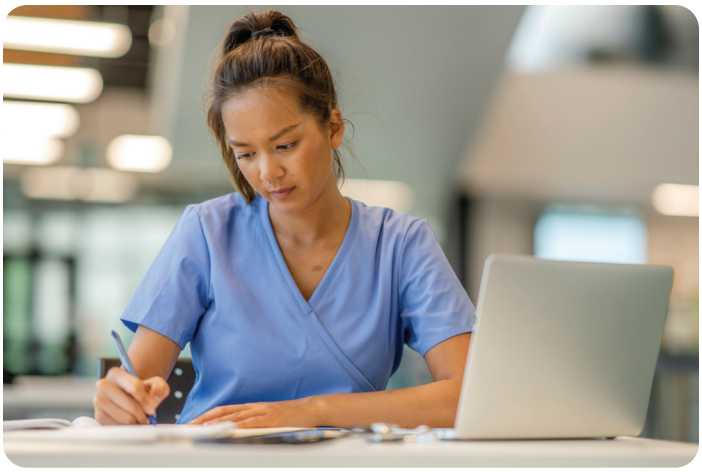
IQVIA's RBM model focuses on centralized monitoring, that consists of continuous reviewing of data and site performance reviews to mitigate risk and enhance trial performance.

This is done along four key avenues:

- **Holistic subject-level review and early signal surveillance:** This increases patient safety by uncovering potential risks earlier and ensuring medical congruency, as well as maintaining protocol adherence
- **KRI Management:** Identifying and managing KRIs and alerts to reduce risk across the whole study
- **Supporting targeted sites to improve site-level dataflow** and assist with CRA visits to increase compliance and risk mitigation
- **Using predictive and advanced analytics** to derive subject, region, country, study, and site level insights in order to find risks before they become issues, to mitigate them entirely

BENEFITS TO END USERS

IQVIA's trio of analytical models provide enormous benefits to end users. The results of an RBM process conducted in this manner speak for themselves. Metrics include a 45% reduction in the number of missing pages in RBM studies versus traditional studies; a 4x lower error rate in critical data compared with traditional 100% SDV4; and improved site communications for a higher overall satisfaction rate with RBM, according to ongoing investigator surveys. Most importantly, RBM studies are able to identify 80+% of potentially missed AEs compared to less than 60% identified in 100% SDV trials.



Conclusion

The new technologies entering the RBM and risk management field have the potential to change and improve almost every aspect of RBM.

Whether a company takes on the task of implementing their own RBM strategies or works with a company like IQVIA to shoulder the task for them, there is a considerable benefit to be gained from initiating the change.

Even beyond new technologies, huge improvements can be made. Integrating centralized monitoring processes into the workflow means increased subject safety, increased data quality, more efficient on-site monitoring, and easier prioritization of critical processes and inherent risks.

With newer technologies, RBM's vast benefits are irrefutable. With tools such as IQVIA's, implementation of RBM processes can transform businesses from a reactive, siloed, and inaccurate process to:

- **one that can predict risks before they occur**
- **reduce costs many times over**
- **fundamentally improve patient lives every day**

The technology is already here and waiting to transform risk management.

[4] https://www.iqvia.com/-/media/library/white-papers/riskbased-monitoring-improves-site-performance-and- investigator-satisfaction.pdf

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