

WHITEPAPER

# The Future of RBM Software

REMARQUE



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# INTRODUCTION

**A** look back at the role of technology in clinical trials shows a succession of systems, each adopted to improve the speed, efficiency, and/or quality of the clinical development process while also reducing costs. Manual processes and paper-based record keeping were eclipsed by technologies such as clinical trial management systems and electronic data capture systems. These technologies made the clinical trials process more automated, (sometimes) faster, and (sometimes) less expensive.

Quality, patient safety, speed, and cost remain top concerns for pharmaceutical companies, medical device companies, and contract research organizations (CROs). Sponsors are under increasing pressure to reduce costs while also shoring up

drug portfolios that have been eroded by patent expirations. CROs, likewise, face pressure from sponsors to reduce costs, yet also move drug candidates safely through trials more quickly. With an eye on speed, safety, and efficiency, CROs and sponsors are employing software that offer enhanced capabilities for identifying risks in clinical trials. The broad category of such systems is often referred to as risk-based monitoring (RBM) technology. But even though such systems introduce new monitoring capabilities, too many fall short of delivering the full benefits of RBM. These shortcomings could represent an incomplete understanding of what RBM means and/or the failure of technology vendors to provide a comprehensive solution that embraces all of what RBM can bring to clinical trials.



# THE RBM APPROACH TO CLINICAL TRIALS

The concept of monitoring clinical trials to assess risk is a familiar one to those in the pharmaceutical industry, but surprisingly, many people in the industry still have a hard time defining it. According to data from a recent report entitled Risk-Based Monitoring Market Assessment from Industry Standard Research (ISR), an independent market research company, more than half of respondents say they are familiar with RBM, but just 1% said they could define it. Part of the challenge has been the inconsistent definitions associated with the term “RBM.”

While the FDA has no formal definition of RBM, it does define monitoring. According to a guidance document from the agency, monitoring involves methods to oversee the collection and reporting of data in clinical trials. Monitoring includes reviewing the study site’s processes, procedures and records, and verifying the accuracy of the data submitted to the sponsor. Moving to RBM, FDA guidance offers a broad perspective on RBM, but falls short of describing what it can offer in clinical development.

So where does this leave the industry? Advances in analytical software capabilities now enable studies using a RBM-based

approach to account for all of the elements critical to assessing and managing risk in clinical trials. Traditional project management employs techniques to manage risk at an operational/execution level, while current regulatory/ethical guidelines identify safety risks. Currently no one process or technology encompasses a single, comprehensive risk management approach. A comprehensive RBM system approaches risk in all of its layers (operational, safety, and quality): risk identification and assessment, risk control and mitigation, risk communication and actioning, and risk review and updating. First, the system should allow the ability to identify and log critical data and processes relevant to the study. There should be the ability to assess and characterize risks both at the start of a study and throughout the course of a study through a built-in risk register. For each of those risks, the RBM software should have the ability to mitigate and control the risks through a variety of risk management strategies.

The risk management strategies employed by the RBM software may be through a combination of automated and manual methods. For example, the software should be able to issue alerts when risks approach established thresholds and/or when safety/data quality is at risk of compromise. More



advanced RBM software may utilize machine learning to alert decision-makers about potential risks not pre-identified during trial set-up. Rather than relying on historical data, which can be misleading and/or out-of-date, a robust RBM system should be able to analyze the prospective data collected during the trial in an ongoing manner to find patterns and anomalies. Furthermore, all of the information in the system should be fully traceable through audit trails.

Detecting risks is only one part of the risk management continuum. A comprehensive RBM software solution should allow for the ability to thoroughly review signals generated in a streamlined and centralized manner through a combination of drill-down capabilities (e.g. geography, site, patient, data item levels), statistical models, and intuitive data visualization. Once reviewed, there should be the ability to action and close the risks through built-in workflows and ticketing functionality. Such functionality should allow for targeted actions to follow-up, close, and prevent such signals in the future.

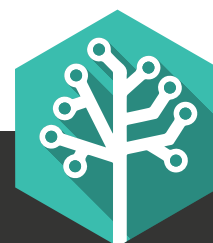
Robust RBM software that is compliant with the upcoming changes to the ICH E6 guidelines should also allow for regular and ongoing review and modification of risks to ensure the implemented risk management activities remain effective and relevant and take into account emerging knowledge and experience. As such, the Risk Register and Risk Mitigation plan may undergo periodic changes that may include additions, modifications, and deletions of items in these instruments.

## A comprehensive RBM system should:

- Approach risk in all of its layers (operational, safety, and quality)
- Allow the ability to identify and log critical data and processes
- Assess and characterize risks both at the start of and throughout the study
- Generate signals through a combination of drill-down capabilities, statistical models, and intuitive data visualization
- Have the ability to action and close the risks through built-in workflows and ticketing functionality
- Allow for targeted actions to follow-up, close, and prevent such signals in the future
- Allow for regular and ongoing review and modification

RBM software with the above capabilities can truly empower sponsors and CROs to conduct trial monitoring efficiently and cost effectively while improving data quality and patient safety.

By remotely monitoring for signals that might require an in-person visit to a trial site, sponsors and CROs can be more judicious about how and when they deploy their staff to sites. Rather than sending clinical monitors to sites at regular intervals, on-site visits can be scheduled only when the RBM system shows that such visits are warranted. This Signal Driven SDV™ approach can help ensure monitoring visits are efficient for the CRA and the site.



# TECHNOLOGY GAPS IN ASSESSING RISK

Automation levels vary from sponsor to CRO to technology provider to RBM software developer to clinical site, and so on. Many involved in clinical development mistakenly believe that “automating” monitoring capabilities or simply rating site risk levels suffice as RBM without realizing that what they have is only a partial risk evaluation. The inconsistent understanding of RBM and business intelligence (BI) tools masquerading as RBM solutions only help to amplify this disconnect.

Beyond technological shortcomings, with partial solutions, sponsors may also fail to fully grasp the scope of the risks they face. Some RBM technologies only look at risk in isolation, without context or analysis. Monitoring systems that fall short of RBM may flag a signal that does not require action, or they may miss a signal that does require action. The limitations of other offerings may lie in their reliance on retrospective data, which means they lack the capability to draw insight from issues that are emerging or place undue

emphasis on historical data not relevant to the current context.

Without a comprehensive solution, implementing RBM is hard, fragmented, and incomplete. An incomplete approach to identifying and managing risk introduces complexity and cost without bringing benefit. Also, a system that incompletely assesses risk could introduce a completely new risk: a false sense of security. Sponsors and CROs may be lulled into a sense that they are participating in risk-based monitoring without fully benefiting from what RBM can offer.

## Shortcomings of some RBM technologies:

- Lack of context or analysis
- Flagging a signal that does not require action or missing a signal that does require action
- Reliance on retrospective data
- Inability to draw insight from emerging issues





# BENEFITS OF A COMPREHENSIVE RBM

Unlike the static approaches of the some monitoring technologies, a comprehensive RBM solution offers a dynamic approach to monitoring and managing risk. Not only does the technology offer a way to view risks, its analytical power provides insight into what the data mean for the clinical trial, while also offering actionable steps that make optimal

use of the data, all wrapped in an audit trail. A comprehensive RBM system does not work in isolation, rather, it works alongside technologies such as EDC and CTMS to integrate data/signals that might call for a monitor to intervene. This technology must be scalable, able to be used with firms of any size that are working on any number of clinical trials.

Implementing RBM comprehensively brings clear, measurable benefits:



**COST.** Clinical monitoring is the largest driver of trial costs (outside of Investigator fees), accounting for an estimated 30% of all expenses in a clinical trial and accounting for over 60% of labor cost in a clinical trial. Rather than the standard practice of scheduling site visits at prescribed times with either 100% SDV or partial SDV not driven by risk signals, RBM analytics can determine when it makes sense for monitors to physically visit a site and can let emerging signals drive the SDV volume, saving on both time and expense. Robust RBM methodology implemented at scale has the potential to save sponsors conservatively between 25% and 30% of the monitoring expense per trial.



**SAFETY AND QUALITY.** While monitoring technologies are available, many fall short of RBM's comprehensive approach, failing to offer insight about developing concerns with safety or data quality. But a comprehensive RBM solution tracks trend information and makes actionable data readily available to sponsors and CROs so they can take corrective action. This can vastly improve both data quality and patient safety.



**IMPROVED TIMELINES.** RBM speeds up the timelines for evaluating study data. At the end of a study, data cleaning adds time (typically >3 months) before the study results can be reported. Each day of delay can cost sponsors millions. With RBM implemented robustly through a comprehensive technology solution, data are evaluated on an ongoing basis, which means that there is minimal delay from the end of the study to the reporting of study results.



**REGULATORY COMPLIANCE.** Regulators are calling for assurances of patient safety and data quality. With the approval of the proposed addendum to the ICH GCP E6 guideline, there will be an increasing need to provide full traceability and assurance when implementing RBM. With robust RBM software solutions, assurance, traceability, and audit should be built-in thus meeting current and emerging regulatory requirements.





# ADOPTION OF RBM

Despite the struggles that some CROs and sponsors have in implementing RBM, many of them have expressed interest in the concept. ISR's survey indicated that nearly a third of studies currently use some form of RBM and that usage is expected to increase to >45% in the next twelve months. Further, a survey of 255 clinical operations leaders indicated that while a third have an RBM initiative in place, about 70% aggregate data manually with spreadsheets and about 90% manually implement their RBM programs.

The proposed addendum to the ICH GCP E6 guidelines incorporates risk-based language into the monitoring practices, specifically calling for a "quality management system that should use a risk-based approach." This approach calls for the following: Critical Process and Data Identification; Risk Identification; Risk Evaluation; Risk Control; Risk Communication; Risk Review; Risk Reporting. While ICH says there may be various approaches to achieving these objectives, the body adds that these approaches could include some combination of on-site and centralized monitoring - a key tenet of a comprehensive RBM system.

## The ICH-GCP approach calls for:

- Critical Process and Data Identification
- Risk Identification
- Risk Evaluation
- Risk Control
- Risk Communication
- Risk Review
- Risk Reporting

These changes only serve to accelerate the adoption of RBM. More importantly, with increasing understanding and clarity around what RBM is, the industry will be able to distinguish between weak RBM solutions and robust, comprehensive RBM solutions.

Going forward, systems that allow sponsors to identify, evaluate, and take mitigating action toward risks will be favored, if not the default standard, for monitoring. This trend favors sponsors and CROs that are taking the time to implement an integrated and scalable RBM technology to monitor and manage their clinical trials.





# CONCLUSION

A comprehensive approach to RBM brings a data-driven approach to clinical trial monitoring. Pharmaceutical companies, medical device companies, and/or CROs that have adopted RBM are already reaping the benefits. More than half of respondents to ISR's study indicated that RBM reduced their clinical trial costs. On average, RBM cut costs by ~15%, according to ISR's report.

While RBM fits with industry goals to reduce costs and ensure patient safety, a comprehensive RBM solution is not a cost reduction strategy alone. Indeed, the most important benefits of adopting RBM are improvements in patient safety and data quality and efficiencies in how clinical trials are conducted. Sponsors and CROs will not realize these benefits until they take a comprehensive approach to their RBM strategy.







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