

# Best Practices for Implementing Risk-Based Monitoring into the Clinical Trial Process





## Introduction

Since the U.S. Food and Drug Administration (FDA) published its industry guidance, “Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring” in August 2013, risk-based monitoring has been a topic of discussion among the clinical research community.<sup>1</sup> However, implementation has been a challenge and adoption has been slow. With the recent updates to the ICH Guidelines for Good Clinical Practice [ICH E6 (R2)], risk-based monitoring is again in the limelight, as sponsors are now tasked with the responsibility of adopting a formal approach to quality management which embraces technology and leverages access to real-time information to drive a more structured approach to risk.<sup>2</sup>

In an increasingly competitive clinical trial landscape, this emphasis on risk is inextricably linked to a focus on patient safety, data quality, efficiency, and cost. Sponsors and contract research organizations (CROs) are under increasing pressure to reduce costs, while moving drug candidates safely through clinical trials more quickly. Adoption of a risk-based monitoring technology can help improve the safety, quality, and efficiency of the clinical development process, while simultaneously controlling costs, but only if the technology provides a comprehensive solution that delivers the entirety of what risk-based monitoring can bring.



## The RBM approach to clinical trials

Monitoring involves methods to oversee the collection and reporting of data in clinical trials. According to the FDA guidance, monitoring includes reviewing the study site's processes, procedures, and records, and verifying the accuracy of the data submitted to the sponsor.<sup>1</sup> ICH E6 (R2) takes this a step further, stating that sponsors should develop a systematic, prioritized, risk-based approach to monitoring clinical trials.<sup>2</sup>

Part of the rationale behind the ICH E6 (R2) update was the need to keep pace with the scale and complexity of clinical trials and to ensure appropriate use of technology. An ICH concept paper emphasized the need to modernize the approach to good clinical practices to enable implementation of innovative approaches to clinical trial design, management, oversight, conduct, documentation, and reporting that would better ensure human subject protection and data quality.<sup>3</sup>

In addition, it was felt that ICH E6 had been misinterpreted and implemented in ways that impeded innovation by emphasizing less important aspects of trials (e.g., focusing on the completeness and accuracy of every piece of data) at the expense of critical aspects (e.g., carefully managing risks to the integrity of key outcome data).<sup>4</sup> A European Medicines Agency (EMA) reflection paper also called for examination of new approaches on the conduct of clinical trials, with established priorities and a risk-based approach with established quality tolerance limits in place.<sup>4</sup>

Risk-based monitoring (RBM) represents a paradigm shift from traditional monitoring. In traditional monitoring, clinical research associates (CRAs) check every data point reported by an investigator against source records with the goal of achieving one hundred percent source document verification (SDV). However, research has shown that SDV is not synonymous with data



quality. Medidata analyzed several thousand studies in its metrics warehouse and found the median percentage of data corrected per trial was only 4.3 percent. When corrections made during the initial entry of each electronic case form (eCRF) were removed, the resulting impact was only 2.7 percent, suggesting that the expenditures made on site monitoring and comprehensive SDV might be disproportionate to the returns in terms of data quality.<sup>5</sup>

RBM utilizes a combination of monitoring strategies, a greater reliance on centralized monitoring and statistical assessments to guide site monitoring visits, and a focus on advanced technical capabilities. With RBM, clinical trial operations and technology are designed to bring together the relevant metrics and data necessary to increase efficiency, safety, and quality to help make data-driven decisions. Targeted monitoring replaces calendar-based visit schedules with

data-triggered visits, concentrating on sites with a higher workload and a greater need for support and monitoring. Centralized remote monitoring and risk-based SDV help reduce the number of data points CRAs must verify against source data on site, reducing workload which leads to a reduction in both time and cost.

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## Not every RBM technology is created equal

Historically, technology advancements, including electronic data capture (EDC) systems and clinical trial management systems (CTMS), have aimed to make the clinical trial process more automated and less expensive. Now, advances in analytical software capabilities enable studies using an RBM-based approach to account for all of the elements critical to assessing and managing risk in clinical trials. While a plethora of RBM technologies exist, many fall short of delivering the full benefits of RBM.

Automation levels vary from sponsor to CRO, and from site to site. 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.

Beyond the technological shortcomings that come with partial RBM solutions, sponsors and CROs 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. Other offerings may be limited in their reliance on retrospective data, lacking the critical capability to draw insight from emerging issues or placing 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 adding





benefit. A system that incompletely assesses risk could also introduce a new risk: a false sense of security. Sponsors and CROs may be lulled into the belief 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

## What to look for in an RBM Technology

A comprehensive RBM system approaches risk in all of its layers – operational, safety, and quality – including:

- Risk identification and assessment
- Risk control and mitigation
- Risk communication and actioning
- 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 or data quality is at risk of compromise. 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 risk-based, signal-driven approach to SDV can help ensure monitoring visits are efficient for both the CRA and the site.

More advanced RBM software may utilize machine learning to alert decision-makers about potential risks not pre-identified during trial setup. 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 act on 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.

To comply with the updated ICH E6 (R2) guidelines, RBM software 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.

RBM software that delivers all of these capabilities can truly empower sponsors and CROs to conduct trial monitoring efficiently and cost effectively, while improving patient safety and data quality.

## 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 act on 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



## Benefits of a comprehensive RBM solution

Unlike the static approaches of 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 means 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 and 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 has the potential to bring clear, measurable benefits:

- **Improving patient safety and data 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.
- **Controlling cost.** Clinical monitoring is the largest driver of trial costs (outside of Investigator fees), accounting for an estimated 30 percent of all expenses in a clinical trial and accounting for over 60 percent of labor cost in a clinical trial.<sup>6</sup> Rather than the standard





practice of scheduling site visits at prescribed times with either 100 percent 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 percent of the monitoring expense per trial.

- **Accelerating timelines.** RBM speeds up the timelines for evaluating study data. At the end of a study, data cleaning adds time – typically more than three 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.
- **Complying with regulatory requirements.** Regulators are calling for assurances of patient safety and data quality. With the approval of the ICH E6 (R2) guideline, there is 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.

## Potential Benefits

- ✓ Improving patient safety and data quality
- ✓ Controlling cost
- ✓ Accelerating timelines
- ✓ Complying with regulatory requirements



## Considerations for implementing an RBM strategy

With ICH E6 (R2), the adoption of RBM will soon become the norm. The risk-based quality management approach outlined in the updated guideline includes:

- Critical process and data identification
- Risk identification
- Risk evaluation
- Risk control
- Risk communication
- Risk review
- Risk reporting

While the guideline states there may be various approaches to achieving these objectives, it emphasizes that these approaches could include some combination of on-site and centralized monitoring – a key tenet of a comprehensive RBM solution.

The move toward implementing an RBM approach requires change management related

to process, people, and technology. The process is encapsulated in a risk-based monitoring plan. Risk assessment remains the foundation of a successful RBM strategy, and it involves:

- Defining the data and processes critical to patient safety and data quality
- Identifying the risks and creating processes to minimize them
- Setting key risk indicators (KRIs) and thresholds that will trigger investigation and/or corrective action

Commitment at the leadership level, along with staff training and a clear understanding of each team member's roles and responsibilities, helps ensure that RBM is built into the fabric of the clinical trial. Looking into the future, software and technology solutions that enable sponsors and CROs to identify, evaluate, and take mitigating action toward risks will be the favored approach, if not the gold standard, for monitoring.



## Conclusion

A comprehensive approach to RBM brings a data-driven, cost-effective approach to clinical trial monitoring. Early adopters of RBM have already seen reductions in their clinical trial costs, with an average savings of approximately 15 percent.<sup>7</sup>

While RBM fits with industry goals to reduce costs, 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 who take a comprehensive, technology-based approach to their RBM strategy stand to reap the benefits.



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## Author

### Michael Arlotto | President

Mike Arlotto is the president of Remarque Systems, Inc. – a software development company formed in 2015 and dedicated to improving clinical trial safety and efficiency. Our first product is Remarque RBM, a comprehensive, purpose-built SaaS platform to design, deploy, and manage risk-based monitoring clinical trials.

Prior to founding Remarque Systems, Mike was the global vice president for Quintiles Corporate Development responsible for transformational partnerships and strategic relationships. Earlier in his career with Quintiles, he led the project management group in North American Clinical Development Services. Mike also managed the proposals, pricing, and contracts groups.

Prior to joining Quintiles in 1997, Mr. Arlotto was a research scientist with Bayer Corp. where he implemented an in vitro metabolism laboratory. He also held the position of Director of Scientific Planning and Development at Dallas Biomedical, a venture capital-backed company that commercialized novel technologies from universities. He was also a founder of OXYgene Dallas, a venture-backed molecular reagent company. Previously, as a research scientist, Mike worked on the application of recombinant enzymes for in vitro drug metabolism and toxicology testing, among other projects. Mike has published dozens of abstracts and articles in research journals and patented a generation of radioactive oxidation products.

Mike earned his Bachelor of Sciences degree in Toxicology at the Philadelphia College of Pharmacy and Science, and a Ph.D. in Toxicology at Kansas University. He completed a post-doctoral fellowship in genetic toxicology at the National Center for Toxicology Research.



Remarque Systems is a provider of risk-based monitoring (RBM) software solutions. Headquartered in Raleigh, NC, with a development center in Indianapolis, IN, Remarque Systems has developed the first fully integrated workflow system to design, deploy, and manage RBM clinical trials.

For more information about Remarque's RBM solution, visit the website [RemarqueSystems.com](http://RemarqueSystems.com) or email [info@RemarqueSystems.com](mailto:info@RemarqueSystems.com). Also, follow Remarque on Twitter [@RemarqueSystems](https://twitter.com/RemarqueSystems) and join our LinkedIn group, [RBM Industry Dynamics](#).