WHITE PAPER

Debunking the Myths of Risk-Based Monitoring for a New Approach to Quality Management

REMARQUE systems

Introduction

Over the past few years, there has been much debate regarding the definition of risk-based monitoring. To put it in context, clinical monitoring – otherwise known as "traditional" monitoring – describes the oversight and administrative efforts involved in monitoring both a participant's health and the efficacy of the investigative drug during a clinical trial. With traditional monitoring, participants visit an investigative site at a given frequency.

Risk-based monitoring (RBM) is a modified resolution of the clinical monitoring schema which employs quality management principles and is characterized by its promotion of a risk mitigation strategy. The quality management principles of risk-based monitoring are centered on conducting a risk assessment, monitoring risks, and mitigating risks as issues arise. But, the overall goal of risk-based monitoring is early detection of issues and proactive risk management.

In the clinical trial setting, risk-based monitoring is a dynamic strategy whereby the extent and focus of monitoring activities are modified based on pre-agreed parameters. Risk-based monitoring may involve a combination of on-site monitoring and remote or centralized monitoring, where technology plays a critical role. Increasingly, risk-based monitoring is regarded as having the most significant impact on improving the quality of both patient safety and study data.

Nevertheless, there are many misconceptions associated with risk-based monitoring in the clinical setting. In this white paper, we focus on debunking five of the most common myths around risk-based monitoring.

Myth No. 1: Risk-based monitoring is a new requirement of the ICH GCP Guidelines

The International Council for Harmonisation (ICH) aims to ensure the effectiveness, safety, and quality of medicines used worldwide by creating a dialogue between regulatory authorities and the pharmaceutical industry. Since the ICH Good Clinical Practice (GCP) guidelines were first developed in 1990, the scale, complexity, and cost of clinical trials have increased. Evolution in technology and risk management processes offer new opportunities to increase the efficiency of clinical trials and focus on the most relevant study activities.

When the original ICH GCP text was prepared, clinical trials were performed using a largely paper-based process. Over the years, advances in the use of electronic data recording and reporting have facilitated the implementation of other approaches. Consequently, ICH GCP has been amended to encourage implementation of improved, more efficient approaches to clinical trial design, conduct, oversight, recording, and reporting, while continuing to ensure human subject protection and reliability of trial results.[1]

With regard to RBM, there are three areas of ICH GCP that have needed updating, namely quality management, oversight, and monitoring. According to the ICH GCP update – commonly referred to as ICH E6 (R2) – sponsors are required to implement a system to manage quality throughout all stages of the clinical trial process.

Quality management

Quality management includes the design of efficient clinical trial protocols and tools, as well as procedures for data collection and processing. ICH E6 (R2) also states that sponsors should focus on those trial activities that are essential to ensuring patient safety and data quality.

The methods used to ensure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. This risk-based approach to quality management is described in detail in sections 5.0.1 through 5.0.7 of the guideline.

Oversight

Section 5.2 of ICH E6 (R2) focuses on the enhancement of sponsor responsibilities related to clinical trial oversight. Sponsors are required to ensure oversight of any trial-related duties and functions carried out on its behalf, including those that are subcontracted to another party by the sponsor's contract research organization (CRO).

Monitoring

Section 5.18 of the updated guideline calls for sponsors to develop a systematic, prioritized, risk-based approach to monitoring clinical trials. This can be a combination of both on-site and central monitoring, but the sponsor must clearly define the rationale for the strategies chosen and document that rationale in the clinical monitoring plan. The flexibility in the extent and nature of the monitoring described in ICH E6 (R2) is intended to permit a varied approach to improving the efficiency and effectiveness of monitoring. It also underscores the fact that a risk-based approach is not one-size-fits-all and should be tailored to the unique requirements of each clinical trial.

ICH and RBM

Clearly, the updates to ICH GCP are about more than just RBM. They are driving a systematic quality management approach to clinical monitoring and study oversight. In the content of ICH E6 (R2), adopting an RBM approach enhances a sponsor's ability to concentrate on patient safety, data integrity, and GCP compliance. RBM adjusts the extent and nature of monitoring to focus on crucial mechanisms and data to encourage value-added work. It also helps to increase inspection readiness.

From an operational standpoint, there are three key steps in implementing RBM:

1. Define a process for identifying risk. TransCelerate has developed a risk assessment characterization tool (RACT), a template that helps identify, manage, and mitigate the risk components of a clinical trial.[2]
2. Monitor risk. With regard to monitoring risk, including a remote monitoring component that provides a view into the data at the patient, site, and study levels is recommended.
3. Mitigate risk. RACT is useful for developing a pre-planned approach to managing issues that may arise and mitigating risk. As mitigation occurs, sponsors must be able to prove that actions were taken. These actions may range from site contact or an on-site visit to a protocol change or other necessary action to ensure patient safety and data quality.

Overall, the entire RBM must be dynamic so sponsors can justify what actions were taken – and why – in response to pre-planned, known, or even unknown risks that may arise during the course of a study. All of these elements need to be addressed when creating a clinical monitoring plan.

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Myth No. 2: RBM is simply reduced source document verification

Source document verification (SDV) is one small aspect of RBM. SDV is the process of confirming the reliability, validity, and accuracy of trial data by comparing original records to reported information to prove that the study can be reconstructed. In a traditional monitoring paradigm, the goal is 100 percent SDV. However, according to a 2014 study, only 3.7 percent of data required correction and only one-third of that data was identified by SDV. Notably, the study also found that approximately 50 percent of site visits were focused on SDV activities, contributing significantly to cost.[3]

RBM aims to improve upon the traditional SDV-focused monitoring model. With RBM, SDV is performed on 100 percent of the data associated with safety and endpoints and less time is focused on the remaining collected data points, allowing more on-site visit time to be utilized on managing identified risks and other issues. While reduced SDV is not a panacea for reducing the rising costs of clinical development, it is an important component. The quality management aspect of SDV – the ability to review data in a remote, centralized manner to detect trends and issues as early as possible and to take steps to address these trends and issues as they arise – is an important component of RBM.

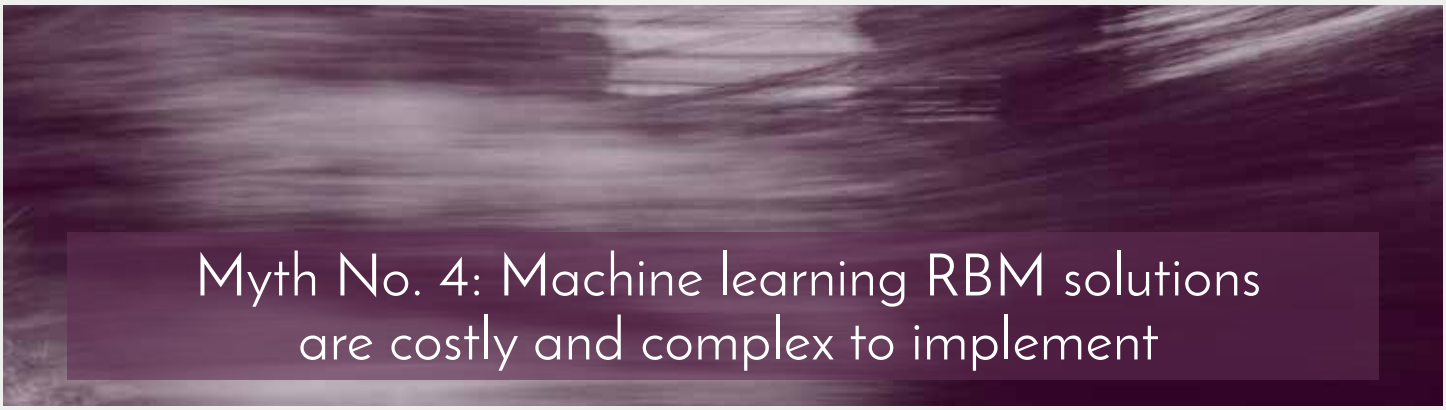
Myth No. 3: Technology alone can solve RBM

Technology plays a critical role in aggregating data from multiple sources and creating meaningful visualizations of that data to get a full view of each patient at every site over time. Like any new procedure, RBM requires people, process, and technology. The most important component is people who are well-trained and who understand the quality management approach. These people must be supported by both a robust process and a technology that not only enables that process, but also is relevant to the roles that people are required to perform.

That technology should:

1. Leverage technology for centralized surveillance
2. Be based on a robust risk assessment
3. Share monitoring responsibilities across all functional areas, including clinical, medical, data management, safety, and statistics
4. Be flexible enough to adjust to changing site demands
5. Rely more heavily on central and off-site monitoring
6. Allow customization of monitoring to site activity and focused trial areas

Figure 1. Requirements for successful implementation of RBM



Myth No. 4: Machine learning RBM solutions are costly and complex to implement

The terms machine learning and artificial intelligence are threatening to some and intriguing to others. While clinical research involves the health and safety of humans and requires direct human intervention, there is a role for machines that have the capacity to analyze and present large amounts of data. The challenge lies in balancing that data processing capability with a simple user interface that trained individuals can use to create actionable recommendations.

There is a cost to implementing RBM, and that initial cost includes personnel training and the implementation of the technology itself. Fortunately, the advent of software as a service has created a flexible approach to RBM without the need for large capital expenditures.

Over time, the implementation of RBM can significantly reduce costs by directing resources to where they are needed most. In comparison to SDV, RBM enables sponsors to focus on critical data and cut down on the number of expensive on-site visits. In addition, the integrated work flows built into RBM enable personnel to easily and quickly turn findings into actions. Through continuous monitoring, patient safety and data quality should improve and the time from last patient visit to database lock should be reduced.

As knowledge improves, machine learning can be leveraged to present recommended actions as issues arise. For example, some systems currently employ a simple user interface to create distance measurements, allowing for the development of algorithms to cluster similar patients and sites. This enables sponsors and study staff to not only relate a given patient to the average or median of a value in a study, but also compare that patient to a similar cluster.

Machine learning can also identify data outliers in a dynamic manner and identify missing data with as little as three patients. As knowledge libraries continue to be built, machines can be trained to understand the nuances of therapeutic areas, disease states, and drug targets. This ability, combined with a robust quality management assessment, can both reduce cost and improve patient safety.

Myth No. 5: RBM cuts clinical investigation out of the loop

In terms of SDV, investigators initially expressed concern that reduced on-site monitoring with an RMB approach would result in an increased burden on site staff. Results have shown that proper training of site personal, procedures to eliminate data handling, and simple-to-use technology can alleviate these concerns.

RBM gives sites the opportunity to be engaged during the process in a time- and cost-efficient manner. Time normally spent on on-site visits can be refocused toward other, more significant aspects of the trial. According to an ISR report, adopting a risk-based approach improved both on-site activity and satisfaction as well as data quality.

Investigators are a critical component of every study, and ongoing communication to keep investigators engaged in the quality management process is an important factor of success.

Conclusion

Much more than source document verification and remote monitoring capabilities, risk-based monitoring offers a streamlined, quality management solution for reducing cost without compromising patient protection and data integrity. RBM proactively addresses risk management, promoting risk mitigation and early detection of issues. By combining risk-based approaches with advancements in technology, RBM helps sponsors implement comprehensive monitoring strategies and focus resources toward the monitoring practices that have the greatest impact on the quality of both patient safety and clinical trial data.

References

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Author

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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

Remarque Systems is a provider of risk-based monitoring (RBM) software solutions. Headquartered in Chapel Hill, 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* or email *info@RemarqueSystems.com*. Also, follow Remarque on Twitter *@RemarqueSystems* and join our LinkedIn group, *RBM Industry Dynamics*.