

Effective Risk-Based Monitoring: THE CRO PERSPECTIVE

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The time has come for the clinical research enterprise to apply risk-based monitoring (RBM) widely to the conduct of studies involving human subjects. The cost, length, and complexity of global trials present an obvious demand for this alternative to more expensive and time-consuming forms of site monitoring. Further, the emergence of technology, including computational capacity and real-time access to multiple data sources and data review, supplies the tools. Finally, recent regulatory guidance provides the green light.¹

Despite the industry buzz about RBM, most organizations have yet to develop standard operating procedures (SOPs) and processes governing its use in the clinical trial process. Moreover, those who have done so face new challenges related to resourcing, quality, and change management.

Recognizing the gap between industry interest in RBM and its adoption levels, players across the investigational spectrum should take a breath and consider what role they can play in enabling successful RBM. As the liaison between sponsors and sites and as central players in the data monitoring process, the staffs of contract research organizations (CROs) are in a unique position to posit improvements that can enhance RBM at every study stage.

The State of the Industry

Although many consider RBM a new concept, it has been evolving for nearly 30 years. Investigators have long used transcription checks as an effective companion (or alternative) to onsite consistency checks in studies where the risk to participants is relatively low, but the momentum propelling broader application of RBM dramatically increased in 2013, with the issuance of final guidance documents on RBM from both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency. Both guidances touted the advantages of the methodology compared to conducting routine visits to all clinical sites and 100% source data verification (SDV).¹

Such support for RBM could not have come at a more opportune time. The average cost of developing a pharmacological asset increased almost 18% between 2010 and 2013, according to Deloitte and Thomson Reuters.² With site monitoring accounting for 30% of total trial expenditures, companies are looking for effective ways to streamline costs.³



In a few short years, RBM has moved from an infrequently used tool to a methodology that everyone is grappling to better understand and apply. For example, TransCelerate, an independent nonprofit created by pharmaceutical and biotechnology companies, has made enormous strides in working to standardize the path to RBM. In 2014, it released an update incorporating lessons learned during pilot studies, and published articles that, among other purposes, analyzed and challenged the value of SDV as a quality control measure.⁴⁻⁶

Experience in several studies shows statistical monitoring can be an effective tool for detecting abnormal patterns that either were not or could not have been detected by onsite monitoring. However, the methodology's data-dependent nature may render it an inappropriate tool for scrutinizing many aspects of trial conduct.

Imperatives for Progress

Despite these advances, RBM remains underused. In 2013, SDV accounted for 85% of data monitoring industry wide, according to Medidata.⁷ If the industry is to realize the full value of RBM and achieve more widespread adoption, it must recognize the barriers in its path and work to overcome them. CROs are uniquely positioned to address those challenges. They are accustomed to working with various types of sponsor companies, ranging from academia and individual investigators to big pharmaceutical and medical device companies, and dealing with their very different objectives, risk tolerance, expectations, and capacity for and familiarity with the RBM paradigm.

If committed to tackle the barriers, CROs can:

- **Foster agreement on a common language.** RBM is routinely described as a “targeted” and “adaptive” methodology employing “remote monitoring” or “centralized monitoring,” but common terminology would ease extensive collaboration both within and across organizations.
- **Knock down silos.** RBM depends on collaborative, crossfunctional teams whose members must have excellent communications and clear understandings of the roles they play in their shared commitment to ensuring participant safety and data integrity.
- **Overcome resistance to change.** Institutions and individuals are often hesitant to abandon long-established processes, to the degree that “sponsor resistance” is reported as one of the chief reasons for slow adoption of reduced SDV.⁸

• **Define quality objectives.** Until they gain skill and experience in adopting RBM, teams are prudent to err on the side of caution in implementing new operating models, but efforts toward improvement should not become bogged down in a quest for nonexistent perfection.⁹

• **Establish metrics.** Although “absence of errors that matter to decision making” may neatly describe a data objective,¹⁰ researchers must determine the means to that end; however, as regulators have provided scant guidance on what level of transcription checking is acceptable, industry leaders are working to develop metrics to assess the success of RBM and gauge quality.

As of October 2014, 10 TransCelerate members had implemented 54 pilot studies to assess metrics focused on quality, efficiency, and cycle time.¹¹ Quality metrics, such as an average number of major/critical audit findings per audited site and percent of unreported, confirmed serious adverse events (SAEs) per site compared to total SAEs, look for quality assurance process benefits because of the improved focus on areas that matter the most.

Some of the efficiency metrics (i.e., an average costs for all types of monitoring per site) evaluate cost impacts. Further, cycle time metrics follow centralized monitoring abilities and indirectly assess early issue identification.

As each company uses its own thresholds, changes in those metrics are also not standardized across organizations, adding to the complexity of the industry-wide evaluation of their effectiveness. As reported by TransCelerate, the majority of the outcomes have either improved or remained neutral; however, some metrics worsened when compared to established baselines.¹¹ Each company should continue evaluating its metrics as they are evolving and may affect the RBM implementation.

Early Involvement is Essential

Research partners must approach studies that call for RBM with an understanding that different members of the team will have varying types and levels of experience with the separate components of RBM, such as centralized monitoring. Partners must share their information and experience as critical input for their monitoring plans, particularly because the industry is still working to develop best practices and standardized policies.

From a CRO perspective, three factors have enormous bearing on the ultimate success of RBM: early involvement, crossfunctionality, and advanced technology platforms.

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LEARNING OBJECTIVE

After reading this article, participants should be able to identify the current challenges within implementing risk-based monitoring (RBM) in clinical studies, and recognize and discuss the role of clinical research organizations in facilitating adoption of RBM across various stakeholders.

DISCLOSURES

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EARLY INVOLVEMENT

RBM requires significant planning. Because it is based on the concept of “quality by design,” a correctly designed protocol and case report form provide the foundation for later monitoring activities.

The FDA encourages sponsors using RBM to proactively describe their monitoring plans. There are recommendations that, when planning for Phase III and IV trials, sponsors should submit plans describing critical variables and the statistical approaches to be used to ensure data quality as early as the end of the Phase II review meeting.¹²

CROSSFUNCTIONALITY

Virtually every aspect of a study can affect its risk at some point—from the study design and defined eligibility criteria to the data collection approach and trial oversight. In RBM, a crossfunctional team comprising clinicians, statisticians, data managers, regulatory advisors, and other experts from both the CRO and the sponsor organization is essential to maintain a focus on quality risk management and the process of data and safety monitoring.

Crossfunctional risk assessment leads to development of different monitoring strategies, all of them including both onsite and centralized monitoring components, but with quite a distinct balance of each, based on the type, phase of the study, status of the investigational product, and many other factors. With RBM, the centralized data review of site risk indicators and data trends becomes a key component of the monitoring strategy in each scenario.

ADVANCED TECHNOLOGY PLATFORMS

Advanced technology platforms and real-time access to critical data are essential to RBM success. Researchers must have platforms that are agile and customizable to the unique needs of each study. In addition, platforms must provide validated processes and tools to ensure consistency. One of the fundamental purposes of these technology platforms is to identify, and account for, through RBM activities, sites at higher risk of experiencing compliance issues, which the FDA defines as “sites with data anomalies or a higher frequency of errors, protocol violations or dropouts relative to other sites.”¹¹

An example of how advanced technology solutions can contribute to balancing onsite and centralized monitoring activities can be seen when “true” e-source data are used. Transcription checking is unnecessary with direct data-entry tools, such as electronic medical records and

patient-reported outcomes. Further, the industry is trying to develop new technologies, such as electronic platforms to replace paper source records, using data generated by wearable devices, which would allow reduction of the overall trial monitoring effort.

The balance of monitoring activities can and should be revised to reflect shifting risks as a study progresses. For example, although monitoring during the enrollment phase may require extensive onsite activities, remote monitoring may become more predominate as a study moves into the treatment phase. Months or even years later, when patients enter a follow-up phase, monitoring may consist exclusively of remote activities. Crucially, if risks associated with the study increase at any point, the combination of onsite and remote monitoring activities can be adjusted accordingly.

CRO-to-Site Lines of Communication are Open

During the second half of 2014, TransCelerate and the Society of Clinical Research Sites conducted focus groups to identify ways sites could enhance quality and RBM implementation.¹² Participants, including study coordinators, principal investigators, and site managers, identified three key measures, saying that sites must:

- develop robust quality plans for staff training and evaluate ongoing site performance;
- conduct study-specific risk assessments to identify mitigations; and
- actively question and discuss the expectations for monitoring with their sponsor and CRO contacts, while still in the feasibility stage.

Although many sites have established processes, and may even have SOPs in place guiding them through the setup and conduct of clinical trials, numerous research-naïve sites lack these fundamentals. According to an Association of Clinical Research Professionals and CenterWatch report, 23% of sites have taken no training action to prepare for RBM, and 45% of sites are not planning for, or implementing RBM.¹³

Where representatives of CROs plan to employ RBM, they must clearly communicate their expectations to site staff and help them design and implement processes to ensure data quality and safety. Everyone must recognize that RBM places new demands on sites while simultaneously reducing the presence of the monitor. These shifts make strong site relationships and effective site



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communication more important than ever. CROs collaborating with the sites provide a closed feedback loop that enables sites to ask questions, report issues, and get answers quickly.

Sponsors and CROs must make sure sites understand the RBM strategies to be applied and what they must do—or do differently—to ensure the success of those strategies. They must conduct training sessions highlighting key study risks and ways to mitigate them. In addition, they must enable sites to educate patients and train their own personnel if staff turnover occurs.

A key element of site training should impress upon site staff the stringency of data-entry deadlines; CROs cannot monitor data remotely unless sites have submitted the data on time. Finally, once the sites embrace it, the RBM methodology will result in sites taking more ownership of the data and research processes, ultimately leading to higher quality data.

Onsite monitors are still important under the RBM approach, but their role differs from what it was under the “traditional” monitoring model. Adapting a reduced SDV approach may still be new to many experienced monitors; however, as any process-oriented functions of clinical trial research, such as training, conducting informed consent, and reporting safety events, are not conducive to computerized review, the RBM model relies upon monitors to track these site-specific variables for any shortcomings. Data consistency, trends, and process quality are more in focus with the RBM model, and the monitor training deployed within the organizations should reflect this approach.

Summary

RBM holds tremendous promise for clinical research. Properly implemented, it will enable sponsors to improve the overall quality and safety of research and help contain drug development costs, but a great deal of learning must take place before the industry can realize its vision for the future.

Although RBM is based on a quality risk-management concept successfully employed in other industries, the clinical research industry is still working to understand and realize its potential. Research partners must build on the current momentum and work with each other to understand and overcome known barriers and devise new strategies.

Toward that end, communication is crucial. For RBM, everybody has something to learn—be it from a colleague in a different functional area, a research partner in a different organization, or a trial site manager in another country. It's time to talk.

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