



The Role of the CRO in Effective Risk-Based Monitoring

The clinical trial industry is evolving. In an effort to improve participant safety and data integrity, regulators are encouraging trial sponsors to transition from a focused on-site monitoring approach they have traditionally employed toward a risk-based approach that utilizes a combination of centralized and on-site monitoring techniques to ensure patient safety and data quality. The Risk-Based Monitoring (RBM) paradigm has many potential advantages over established monitoring practices including enhanced patient safety and data integrity, more efficient and effective protocol design, reduced costs, and the ability to strategically adjust oversight in keeping with changes in risk level.

Realizing the potential of RBM requires early planning, analytical expertise, sophisticated tools and process adaptability. Deep cross-functional expertise early in the trial process enhances the ability to assess overall risk, define critical data and processes, develop an integrated plan for addressing risk, and execute a monitoring plan that meets the trial's unique requirements.

The appeal of RBM

In clinical research, the status quo isn't good enough. Rising costs, increasingly complex trials, and pressure from regulators to adopt monitoring techniques that more effectively identify and mitigate risk have led to a groundswell of support for RBM. In 2011 the U.S. Food and Drug Administration, the European Medicines Agency and the United Kingdom's Medicines and Healthcare Products Regulatory Agency all issued papers intended to "open up the discussion on approaches to clinical trials and to new thinking, in order to facilitate the development of proportionate clinical trial processes."^{1,2}

In August 2013 the FDA issued final guidance on the subject emphatically noting, "There is a growing consensus that risk-based approaches to monitoring, focused on risks to the most critical data elements and processes necessary to achieve study objectives, are more likely than routine visits to all clinical sites and 100% data verification to ensure subject protection and overall study quality."³ Adding to RBM's appeal is its welcome potential to reduce trial costs by as much as 15-20%.⁴

The power of RBM lies in risk identification and strategic vigilance. While current on-site monitoring generally takes an even-handed approach to risk by emphasizing 100% source data verification (SDV), RBM is laser focused. RBM considers each research program holistically, identifies areas of increased risk and uses that information as the basis for a customized monitoring program. RBM isn't static. If risk levels increase at any phase or stage of a study, monitoring can quickly be intensified.

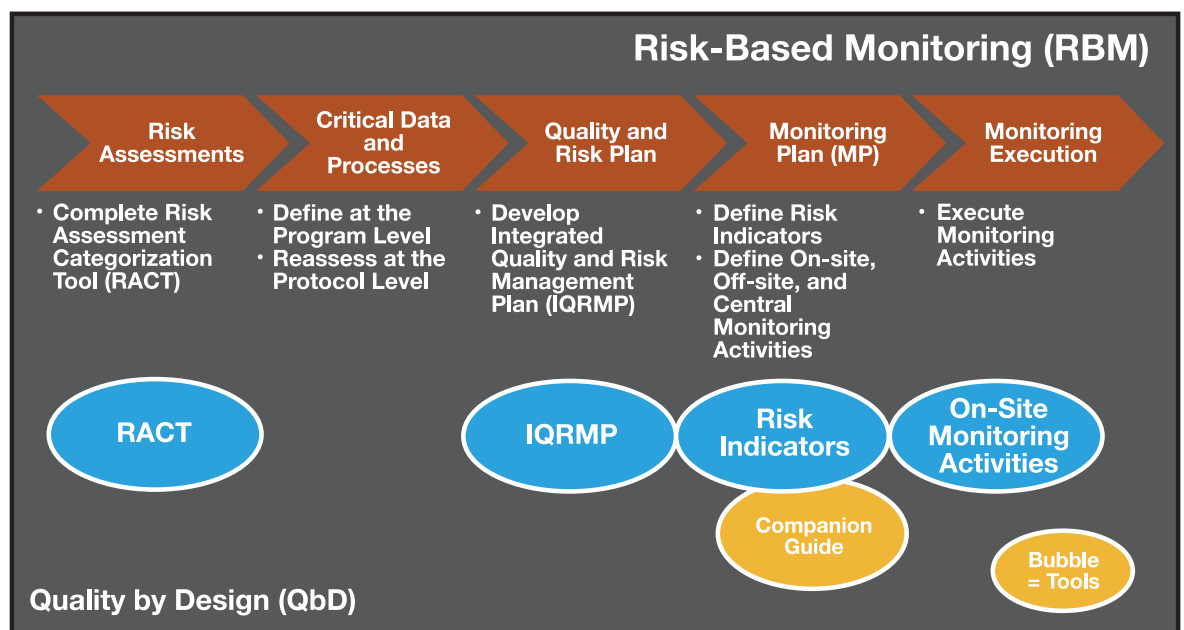
While some of the verbiage associated with RBM may be new, the approach has been evolving for some time. For many years researchers have applied RBM methods in clinical research studies where the risk of participation is relatively low, such as those evaluating approved drugs with well-known safety profiles or those focused on data collection.

But the prospect of applying RBM more broadly is only now gaining traction. The on-going development of sophisticated analytical tools and processes, formal FDA guidance and several high-profile industry initiatives are propelling the RBM movement into overdrive. Initiatives undertaken by the Clinical Trials Transformation Initiative (CTTI) and TransCelerate Biopharma Inc. have attracted wide-spread industry attention and help describe how RBM principles might be operationalized.

CTTI, a public-private partnership working to find ways to increase the quality and efficiency of trials, has devised a Quality by Design (QbD) approach that focuses oversight on the errors most likely to adversely affect trial quality. QbD holds that sponsors and regulators should agree up front on critical data points requiring verification. Based on that assessment, sponsors can create a quality risk management plan that can be reviewed, adapted and amended during the course of the trial to reduce risks.⁵

TransCelerate, an independent non-profit created by pharmaceutical and biotechnology companies to improve the development process, has focused on standardizing the path to RBM. Until now individual sponsors and their research partners have addressed RBM issues on a project-by-project basis. The TransCelerate model presents a consistent approach that aligns with QbD principles. The model can be adopted industry wide and is scalable to any phase of a study.

Outlined in the graphic below, the methodology, which TransCelerate member companies are piloting in a variety of trials, focuses on risk-based central and off-site monitoring activities, rather than routine site monitoring visits, as a way to identify potential issues sooner.⁶



[Source: TransCelerate]

Translate theory into practice

Because successful RBM depends on an integrated approach to risk assessment and monitoring throughout the entire project lifecycle, collaboration and communication are critical.

Sponsors and their research partners should begin planning for RBM at the outset of the research process to ensure processes are aligned across the organizations and determine who will handle various monitoring activities. All parties share an unwavering commitment to ensuring participant safety and data integrity.

It's essential to recognize that RBM is not a "short cut" to monitoring and managing risk but a more efficacious approach to vigilance. RBM is not "reduced" monitoring, it is strategic monitoring based on technologically-enabled, risk-based algorithms that focus monitoring resources on the locations and activities where they are most needed. What's more, an effective RBM program may include multiple types of monitoring activity, including traditional on-site verification. In many cases on-site monitoring may be the only viable way to ensure adequate protection of the rights, welfare and safety of human subjects and the quality of study data, and will be an important component of the overall monitoring plan.

The TransCelerate model provides valuable guidance in describing how sponsors can work with their CRO partners to put RBM principles into practice. The TransCelerate methodology begins at the program level. Sponsors are encouraged to conduct a holistic, cross-functional risk assessment to ascertain risks common across all studies in a given program and establish an initial list of critical data requirements.

Next, sponsors work with their service providers to jointly assess risks more thoroughly at the protocol level and expand the initial list of critical data. Partners should consider issues such as the impact and likelihood of error, appropriate mitigation activities, and the degree to which potential errors would be detectable.

CRO involvement is essential at this stage to ensuring research partners are working from common assumptions and quality benchmarks. A CRO with deep therapeutic, regulatory and operational expertise facilitates the risk-assessment process by highlighting items within the protocol design that have the potential to impact overall risk levels. Identifying these risks and potential operational challenges early in the process is essential to the success of RBM later in the study.

Having assessed risks and defined critical data and processes, a cross-functional team comprised of players from the sponsor and CRO organizations should craft an Integrated Quality and Risk Management Plan (IQRMP). It is important to understand that all of the individual plans contained in the IQRMP should trace their roots back to the risk assessment. What's more, while the monitoring plan is a key component of the IQRMP that provides detailed instructions for oversight through every step of the trial, it shouldn't be considered in isolation. Under the RBM paradigm the relevant expectations should be covered in other functional study plans as well (such as the data management plan), to ensure a true cross-functional approach to risk assessment and data monitoring.

Monitoring activities: Striking the balance

In many cases on-site monitoring will remain a critical aspect of the overall oversight program. The value and efficacy of RBM depends on striking the proper balance between on-site and centralized activities. Sponsors must work with service partners to devise a plan that meets expectations for quality data, using remotely conducted activities where feasible, as well as optimizing on-site time and ensuring focus on critical elements of the study.

The FDA clearly states, "No single approach to monitoring is appropriate or necessary for every clinical trial. FDA recommends that each sponsor design a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. Ordinarily, such a risk-based plan would include a mix of centralized and on-site monitoring practices."²



Ideally, monitoring activities at each stage of a trial should be aligned with the overall risk level assigned at the protocol level and augmented as necessary should risks increase. As a practical reality however, many companies take an overly conservative approach to on-site monitoring by requiring 100% SDV. However, this does not guarantee patient safety or data quality as the review is focused on individual data points versus a well-rounded review utilizing a combination of different methods. A more comprehensive approach needs to be supported by technical tools and processes that can be quickly adapted to the changing needs of a study/program.

Partnering with a CRO

While industry-wide implementation of RBM is in its infancy, it is undoubtedly on a growth track. To maximize its benefits and ensure optimal oversight, sponsors need to partner with CROs that have the core competencies necessary to conduct RBM. The critical capabilities a CRO must bring to the process include:

- **Therapeutic, operational and regulatory expertise.** Risks can arise at any stage of a study from many quadrants: from the initial protocol design bearing significant operational challenges to protocol amendments following the availability of the new data; enrollment challenges requiring engagement of the additional centers and geographies; shifting regulatory climate and increased requirements from the competent authorities. Your CRO should provide comprehensive cross-functional expertise to help you effectively identify, mitigate and monitor risk throughout the study duration.
- **Flexibility.** Because risk levels differ from one aspect of the trial to the next and may fluctuate, adaptability is critical. CRO team members must be as adaptable as the technological tools they employ to adjust to changes that arise during a study.
- **Strong site relationships.** Both on-site and remote site communication play an equally important role in the monitoring process. However, as the RBM model relies increasingly on the centralized activities, and given the reduced “face time”, strong site relationships based on ample training and clear communications are even more critical. Partnering with CROs that have strong site alliances has always been important, but the RBM paradigm raises the stakes. RBM places new technological, training and data-entry expectations on the sites. Your CRO is responsible for making sure sites have the tools, training and feedback they need to implement RMB effectively. The CRO team must be in direct contact with sites following the review of trends and individual site data.
- **Superior technology and analytical capabilities.** CROs must demonstrate a superior ability to identify, collect and analyze data. A very close communication and cross-functional coordination is required to identify trends and act quickly to implement appropriate targeted monitoring activities. These are alien skills to some companies accustomed to operating under the traditional monitoring model. Your CRO should be able to demonstrate that it has invested in the training and analytical tools necessary to support the emerging RBM paradigm demands.

The road ahead

RBM is an evolving paradigm and one that will require new skills and thinking on the part of stakeholders across the clinical research spectrum. The proliferation of technological advancements enabling companies to collect, process and analyze large volumes of data in real time is only a foreshadowing of the opportunities that lie ahead. While change can be difficult, it is incumbent on the industry to embrace a methodology that promises to enhance patient safety and improve data integrity.

RBM is clearly the direction for the future and stakeholders need to position themselves for the brave new world it represents. Sponsors should start working with their CRO partners early in the research process to identify and so as to develop optimal monitoring strategies. Service providers must assess and refine their research process to identify and develop optimal monitoring strategies.

The finer points of RBM haven't been hammered out and its adoption will be a gradual process. Despite these caveats and unknowns, stakeholders must proactively begin to consider how to incorporate RBM into their operations as they look to the future.

About the author

Alexander Artyomenko, MD, PhD, Global Director, Late Phase Clinical Operations

Dr. Artyomenko has over 12 years of experience in Late Phase clinical research. His unique background encompasses both medical practice and clinical research and development, with a highly successful record in planning and executing Phase IIIb-IV studies. Dr. Artyomenko has developed strategies for global trials in a variety of therapeutic areas for both pharmaceutical and medical device products. Dr. Artyomenko is an expert in global regulatory affairs concerning post-marketing and observational studies, including epidemiology, expanded access/compassionate use programs, health economics and outcomes research, and registries.

About Medpace

Medpace is a global full-service clinical research organization providing Phase I-IV core development services for drug, biologic, and device programs. With more than 1,400 employees and clinical trial experience in over 40 countries, Medpace has the global reach and capability to conduct studies and navigate regulatory requirements worldwide. In addition to Phase II-IV development services, Medpace provides Phase I / IIA clinical services from Medpace Clinical Pharmacology, central laboratory and therapeutically specialized testing from Medpace Reference Laboratories, complete bioanalytical services in all stages of drug development from Medpace Bioanalytical Laboratories, centralized imaging core laboratory management and reading from Medpace Imaging Core Lab, and medical device development from Medpace Medical Device.

Reference:

- ¹ EMA. Reflection paper on risk based quality management in clinical trials (EMA/INS/GCP/394194/2011). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500110059.pdf. Accessed Aug, 16, 2013.
- ² MHRA. Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products. Available at: <http://www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf>. Accessed Aug, 16, 2013.
- ³ FDA. Guidance for industry: Oversight of clinical investigations – A risk-based approach to monitoring [August 2013 Procedural]. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf>. Accessed Aug, 16, 2013.
- ⁴ PWC. Risk-based monitoring: Reduce clinical trial costs while protecting safety and quality. March 2013. Available at: http://www.pwc.se/sv_SE/se/bioteknik/assets/risk-based-monitoring-reduce-clinical-trial-costs-while-protecting-safety-and-quality.pdf. Accessed Aug, 16, 2013.
- ⁵ Clinical Trials Transformation Initiative. Results and recommendations: Effective and efficient monitoring as a component of quality assurance in the conduct of clinical trials. Available at: <https://www.ctti-clinicaltrials.org/website-administration/documents/Monitoring%20Project%20Results%20and%20Recommendations%20FINAL%20090311.pdf>. Accessed: Aug.16, 2013.
- ⁶ TransCelerate BioPharma Inc. Position paper: Risk-based monitoring methodology.