Risk-based Monitoring: The Innovative Model Redefining Clinical Trial Risk Management

PEER REVIEWED

Over the past two decades, clinical trials have grown increasingly burdened by new layers of complexity[1] and associated costs. In response to these shifts, stakeholders across the industry have been working to find ways to reduce complexity and cost to bring medications to patients faster.

One area in the clinical trial process that has been identified for improvement is risk-based planning and management. Monitoring and managing risk has always been a critical piece of clinical research, as it directly relates to the safety and evaluation of the efficacy of a drug. However, historical models of clinical trial risk management have had many limitations.

This article spotlights a modern, risk-based approach to the design, planning and management of clinical trials, known as **Risk-based Monitoring** (RBM), exploring its key attributes, technology needs and relationship to health authorities, as well as its potential to improve quality, safety and efficiency.

Limitations of Traditional Clinical Trial Monitoring and Management

Historically, clinical trial sponsors conducted monitoring via frequent (often every four to eight weeks) in-person visits to the sites where the clinical trial was being conducted. This approach relied heavily on source data verification (SDV), a cross-reference check of the data recorded in a case report form against the original source of information, such as a medical record. While the SDV and frequent on-site evaluation approach did provide a level of generalised quality control to ensure subject safety and reliable data integrity, it was a reactive method – meaning it had limited ability to proactively identify and address significant potential risks to safety and data. Limitations associated with this traditional method of monitoring include:

- Perpetual backlog and lags in the review of site data due to delays in data entry and the lack of near real-time data integration and reporting.
- Its resource-intensive nature.
- Typically, monitoring being applied uniformly throughout a trial rather than proportionate to risk.
- Limited ability to pro-actively identify and prevent issues from recurring.
- Research indicating that the use of 100% SDV is not effective at uncovering or preventing risks.[2]
- The high cost of on-site monitoring and SDV is disproportionate to the value gained.

Recognising these inefficiencies, and the significant advances in technology to enable a new paradigm, there was a movement in the R&D industry – advocated for by the FDA and other global health authorities, and championed by industry groups (e.g. CTTI, TransCelerate, AVOCA and other consortia) and some biopharmaceutical companies – to develop a new risk-based approach focused on risks and errors that matter.

Risk-based Monitoring: The New Paradigm

The shift from traditional monitoring to RBM is predicated on the use of off-site and centralised monitoring mechanisms enabled by regular, ongoing data surveillance to monitor important study parameters. It also integrates adaptive on-site monitoring to further support and evaluate site processes, subject safety and data quality. The combination of these elements when coupled with robust up-front and ongoing risk assessment, planning and management activities, drive a more comprehensive, proactive and risk-driven monitoring methodology.

Fundamental to RBM are several component:[3]

- **Building quality by design (QbD) into trials during protocol development** to ensure that processes and associated data acquisition are focused on what is critical to the study and its subjects, and is executed in a way that mitigates errors which would have the greatest impact on subject safety and data quality.
- **Early and ongoing risk assessment** – a process carried out to assess potential risks that could affect subject safety, data quality or regulatory compliance, and identify how they will be managed cross-functionally within an integrated quality risk management plan (IQRMP).
- **A focus on critical processes** (processes critical to the reliability of the study findings, subject safety and/or ethical conduct) and **critical data** (data critical to the reliability of study conclusions, subject safety and/or related to the evaluation of protocol compliance).
- **Use of risk indicators,** which denote metrics used to identify risk exposure over time, as well as thresholds, the level, point or value associated with a risk indicator that will trigger an action.
- **Adjusting monitoring activities on a continuous basis**, based on the issues and risks identified throughout the course of the study.
- **Shifting from SDV to SDR**. Source data review (SDR) is the review of source data/documentation for protocol compliance and quality of source, ascertaining investigator involvement and appropriate delegation, and assessing compliance to Good Clinical Practice (GCP) and relevant regulations.
- **Digitising clinical data,** enabling the earlier detection of data quality issues through regular, targeted data surveillance, leveraging technology advances in the capture, integration and analysis of near real-time data.

RBM refocuses monitoring efforts towards the areas with the greatest risk and need, leading to increased overall effectiveness and potentially lowered costs by reducing the effort on low-value activities. Many in the industry are confident that this risk-based approach, its elimination of inefficiencies and movement towards centralised data monitoring will have important benefits to the entire clinical trial ecosystem.[4]

The Impact of RBM on Clinical Research and its Stakeholders

RBM supports clinical trial success by improving quality data collection, supporting patient safety and promoting efficiency across multiple processes. Supporting these primary benefits are a number of more granular improvements that warrant consideration:

- **Improved protocol quality and reduction of complexity** achieved through the early assessment of risk and increased

focus on what is critical to the study to enable quality by design (QbD).
- **Reduction in efforts** expended on low-value activities (e.g. 100% source data verification).
- **Earlier detection of issues**, with a greater focus on identifying root causes to prevent recurrence.
- **Cost reductions** through more focused centralised monitoring activities.
- **Ensuring a study is compliant with the protocol**, Good Clinical Practice (GCP) principles,[5] and relevant regulatory requirements.
- Engendering a **more collaborative and aligned** cross-functional team approach. The RBM methodology facilitates the coordination of monitors, data managers, statisticians, medical monitors and site staff.

Further, RBM has specific and important positive implications for various stakeholders in the clinical research enterprise:

- **Investigator sites:** RBM's regular, recurring data surveillance prevents a mass generation of queries, which in the past have been issued months or years after the data was generated. RBM can also help site personnel focus on their core job functions by reducing time spent on administrative tasks while also improving inspection readiness.
- **Health authorities:** A proactive risk-based approach to clinical study planning, management and oversight is well aligned with regulatory expectations for the conduct of clinical trials.
- **Sponsor companies:** RBM more efficiently allocates resources while improving data integrity and GCP compliance.
- **Patients:** RBM helps patients participating in a trial through the shift in focus to critical data and processes, which is inextricably tied to patient safety. Further, with reduction in protocol complexity and the streamlining of certain administrative tasks, site staff have more time to focus on patients and their trial experience.

Technology Needs

Technology – specifically, its ability to support data integration – can be an important component of implementing RBM. While functional plans are tailored to the available technology in a trial, there are several enabling technologies that may be considered:
- A source-agnostic data model that can be mapped to a source system data model.
- A mechanism for mapping and aligning key data as part of its integration components, namely the ability to harmonise the data to a common target.
- The ability to map data into a format that enables efficient generation and management of risk indicators and metadata management.
- Extensive data-sourcing capabilities, with a scalable infrastructure that supports multiple integration formats and can integrate with internal systems within a corporate firewall.
- Features that enable the defining and monitoring of data validation – which will help support data consistency and integrity.
- A full data lineage that traces each data point from its origin through data integration to its usage in the user interface and risk indicators.
- Robust analytical capabilities to enable data surveillance and the identification of outliers and trends.
- The ability to document and manage risk and issues through their life-cycle to resolution.

Technology used for RBM should ideally support a directed, data-driven, risk-based approach that acquires and provisions data from multiple sources. This enables users to conduct central monitoring by triaging signals identified via risk indicators through a targeted review of relevant data and adapting monitoring activities accordingly. There are several values ideal to RBM technology, which are detailed below.

- Since the goal is to ensure efficient remote monitoring, risks and issues should be managed holistically in a single system, including the effective integration of disparate data sources and formats.
- Additionally, to ensure rapid identification of outliers and trends in large data volumes, the development of relevant analytics, along with consistent documentation of risk and issues is key.
- As risks and issues are identified and actions are taken to resolve them, it's critical that a system retain that information so that it's accessible for learning purpose and future enhancements. In this way, technology can contribute to RBM's additive, evolving nature, particularly when root causes for these issues are being captured. This also provides traceability to regulators for how risks and issues were managed through the conduct of the trial.
- Last, technology should enable secure, role-based access to data, with sponsors controlling which roles have access to which levels of data – programme, study, site and so forth.

Specific technology systems that an RBM methodology could integrate are electronic data capture (eDC) systems, third-party clinical data providers (e.g. Central Laboratory), issue management or clinical trial management systems (CTMS), electronic trial master file (eTMF), interactive response technology (IRT), electronic patient-reported outcomes (ePRO), quality management systems, along with eConsent and eSource technologies. Also worth underscoring is the complementary potential of mHealth devices and sensors to enhance the capability for near real-time data acquisition and surveillance in an RBM model.

Since RBM is still evolving and clinical trials often involve multiple stakeholders (sponsors, CROs, other third-party vendors), successful technology solutions will be ones that are also malleable to the changing landscape.

It is important to raise, in the context of technological integration, the value of data integrity in effective risk management plans. According to the World Health Organization's Guidance on Good Data and Record Management Practices,[6] data integrity is the degree to which a collection of data is complete, consistent and accurate throughout the data life-cycle. The effectiveness of off-site and centralised monitoring, two pillars of RBM, is contingent upon data being entered in a timely manner and being remotely accessible.

Global Health Authorities: Involvement and Perspective

Health authority opinions on RBM have been primarily supportive. In 2011, the FDA,[7] the European Medicines Agency (EMA)[8] and the United Kingdom's Medicines and Health Products Regulatory Agency[9] (MHRA) released guidance papers on RBM, reflecting their support for the shift from historical clinical development models which were highly dependent on monitoring resource-intensive site monitoring visits to a more proactive, holistic, risk-based approach.

In 2013, the FDA issued additional guidance, this time solidifying its position that RBM is better able to ensure subject safety and data quality compared with approaches centered around SDV and on-site monitoring. Further, in 2016 the International Council for Harmonization of Technical Requirements for Human Use (ICH) E6 Guideline for Good Clinical Practice (GCP) revision[10] reinforced

the growing regulatory expectation for sponsors to implement risk-based oversight consistent with the RBM methodology.

The Future of RBM

In exploring the potential impacts that RBM has had thus far on clinical research effectiveness and efficiency, it's also important that the future of RBM be examined. Below are three primary considerations for the next phase of RBM.

Evolution of Technology Solutions

Successful implementation of an RBM methodology is predicated on a combination of the right people, processes and technology. Since RBM technology is still relatively new and rapidly changing, in the future, successful technology solutions will have to adapt to meet the needs of future clinical trial environments. A balance of immediate and long-term considerations is essential.

At the moment, RBM relies on technology to support activities related to risk assessment and cross-functional risk mitigation planning, risk indicator data review, data integration and analysis, and risk and issue tracking and management. Ideally, RBM systems in the future will further excel at each of these areas while enabling increasing levels of knowledge management. As the needs around these activities evolve, companies must support scalable implementation, meaning RBM systems can integrate with independent complementary systems.

Integrating Change Management

Change management, the practice of aligning values, culture, people and behaviours to new modes of operation that can reshape an organisation, is critical to future success of RBM. Proper change management in the context of RBM includes educating and engaging new and potential adopters about the nuances of RBM, debunking myths surrounding RBM, and creating awareness campaigns and comprehensive training tailored to key stakeholders. Essential to effective adoption of RBM is a shared understanding of terminology, scope of tasks, and roles and responsibilities across the entire stakeholder ecosystem.[11]

Identifying the Right Metrics

Clear and defined metrics would greatly help to assess and further quantify the benefits of RBM implementation in the long-term. The value of centralised monitoring and the pathway to more widespread RBM understanding will be enabled by this definition of, and agreement within, the sponsor company and investigator site on critical success factors. Key to this is encouraging sponsor companies, investigator sites, CROs and technology companies to openly publish and share successes, failures, and lessons learned of various RBM models and technological solutions.

While metrics can be complex, sponsor companies could consider measurements related to increased data quality, reduction in compliance risk or fraud detection, better relationships with sites, and cost efficiencies.

With increased adoption and collection of well-defined, RBM-relevant metrics, organisations will have the ability to measure and evaluate performance in a quantitative rather than qualitative manner, and make adjustments to their RBM approach as needed, supporting increased success in the future.

RBM's Story is Just Beginning

The continued enthusiasm around risk-based monitoring and its growing support among clinical trial stakeholders is evidence of the limitations of traditional monitoring centred around SDV and on-site monitoring. In its ability to reduce historical and common pain points, and inject innovation into the process, RBM is improving subject safety and data quality as well as contributing to regulatory compliance and reducing burdens and costs.

The growing adoption within industry, coupled with the guidance from regulatory authorities, indicate the staying power of the RBM methodology. Technological advances related to big data integration and analytics, mHealth, e-Source and artificial intelligence (enabled by increasing digitisation of clinical and operational data and associated metadata), will further enhance the RBM paradigm and its potential to generate significant and lasting positive impacts on clinical research.

REFERENCES

1. US Food and Drug Administration. Guidance for Industry Oversight of Clinical Investigations-A Risk-Based Approach to Monitoring. 2013. <http://www.fda.gov/downloads/Drugs/Guidances/UCM269919.pdf>
2. TransCelerate BioPharma. Evaluating Source Data Verification as a Quality Control Measure in Clinical Trials; Therapeutic Innovation & Regulatory Science, November 2014; vol. 48, 6:pp. 671-680., first published on October 9, 2014 <http://journals.sagepub.com/doi/pdf/10.1177/2168479014554400>
3. TransCelerate Risk Based Monitoring Interactive Guide. 2017.<http://www.transceleratebiopharmainc.com/rbminteractiveguide/what-is-risk-based-monitoring-rbm/introduction/>
4. Clinical Leader. Risk-Based Monitoring: A More Strategic Approach to Site Monitoring and Clinical Data Management. June 8, 2015. <https://www.clinicalleader.com/doc/risk-basedmonitoring-a-more-strategic-approach-to-site-monitoring-and-clinical-data-management-0001>
5. US Food and Drug Administration. Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance. 1996. <http://www.fda.gov/downloads/Drugs/Guidances/ucm073122.pdf>
6. World Health Organization. Guidance on Good Data and Record Management Practices. 2015. <http://www.who.int/medicines/areas/quality_safety/quality_assurance/Guidance-on-good-data-management-practices_QAS15624_16092015.pdf>
7. US Food and Drug Administration. Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring (Draft Guidance). 2011. <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/UCM277529.pdf>
8. European Medicines Agency. Reflection paper on risk based quality management in clinical trials. 2011. <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500110059.pdf>
9. Medicines and Health Products Regulatory Agency. Riskadapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products. 2011. <https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf>
10. International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH): Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2), 9 November 2016. <http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf>
11. Meeker-O'Connell. Update on clinical trials transformation initiative (CTTI) quality-by-design project. DIA Quality

Justin Stark

Head/Director Risk Based Monitoring & Standards, UCB, & TransCelerate BioPharma RBM Initiative Leader