

THE EVOLVING ROLE OF THE CLINICAL TRIAL MONITOR AND STUDY TEAM MEMBERS IN THE AGE RISK BASED MONITORING (RBM)

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ABSTRACT

BACKGROUND

Clinical trial monitoring is broadly based on protecting the rights and the well-being of the human research subjects, overseeing the progress of the trial, and ensuring that the trial is conducted in compliance with the applicable regulations, SOPs and study documents^[1]. The systematic application of the recently introduced Risk Based Monitoring (RBM) technique is facilitating a collaborative vigilance approach, and a new definition of clinical trial monitor is evolving. A clinical trial monitor no longer seems to be a single entity but a group of people from cross functional teams that share joint accountability for overall data monitoring and quality governance framework.

OBJECTIVE

To explore the evolving role of a clinical trial monitor and other key study team members in the Risk Based Monitoring landscape.

METHOD

A literature search was conducted, followed by several discussions and brain storming sessions with key functional study team members currently working in the RBM pilot trials. Some limitations with this methodology were a lack of available literature specific to the topic under study, as well as the lack of sufficient industry experience in the implementation of the RBM practices at present.

CONCLUSION

Conventional monitoring was based mostly on data review in silos by the monitors. RBM and the associated technologies have created an opportunity to assess the study and center specific risks at each level of the data hierarchy by the appropriately qualified study team members for a continuous governance of clinical study data. The roles and responsibilities of these core study

team members are continuously shifting and it is likely that this shift, along with training and continuous adaptation, will re-define the face of a clinical trial monitor while also leveraging the quality of clinical trial outcomes overall.

A clinical trial monitor role has been critical to ensuring the rights and well-being of the clinical research participants, and assuring the scientific integrity of the data collected. Before the advent of Risk Based Monitoring (RBM) and associated technological interfaces, a monitor had been the one that was typically engaged in the review of individual subject related data points embedded in the case report forms (CRFs). Additionally, in the traditional setting, frequent on-site monitoring with 100% source data verification had been deemed as the “gold standard” for [2] [3] meeting regulatory obligations. Through these on-site monitoring visits, the clinical trial monitor had been assessing and reporting non-compliance, data related errors, and trends at a specific site or sites via on-site monitoring of the data. The key challenges with this approach had been that monitors were reporting mostly data recording and site procedural compliance related errors based on review of the subject data during their visit to the centers. These assessments had been specific to the centers assigned to them and not a holistic view of all the data for the entire study. Additionally, this approach did not address the study design or analytical types of errors.

There has been a correlation between these challenges and the fact that, over the last several years, the types and nature of deficiencies identified through the regulatory inspections have not changed much^[4]. Lack of systematic quality assurance and governance throughout the life cycle of a clinical trial has been at the crux of these challenges. RBM may have brought that paradigm shift for the clinical trial industry. Four prominent organizations (CTTI, EMA, FDA and PMDA) and TransCelerate’s initiative^[5] have contributed to the evolving concept of RBM by providing [2], [4], [6], [7] guidance in the context of risk and quality assurance between 2008 and 2013.

The FDA issued guidance for the industry on the “*Oversight of Clinical Investigations-A Risk-Based Approach to Monitoring (RBM)*”^[4] makes it clear that sponsors can use a variety of approaches to managing data quality through technology enabled data driven actions, by targeting monitoring activities to where they will deliver the best benefit to the study and patients. This guidance has generated a keen interest among the sponsors and clinical trial sites about its implications and adaptability. Sponsors are diligently working on successful implementation of these strategies. Currently there are 54 active RBM trials (Phase I-IV) that have begun to utilize the TransCelerate RBM methodology across 10 sponsors, within multiple therapeutic areas^[5].

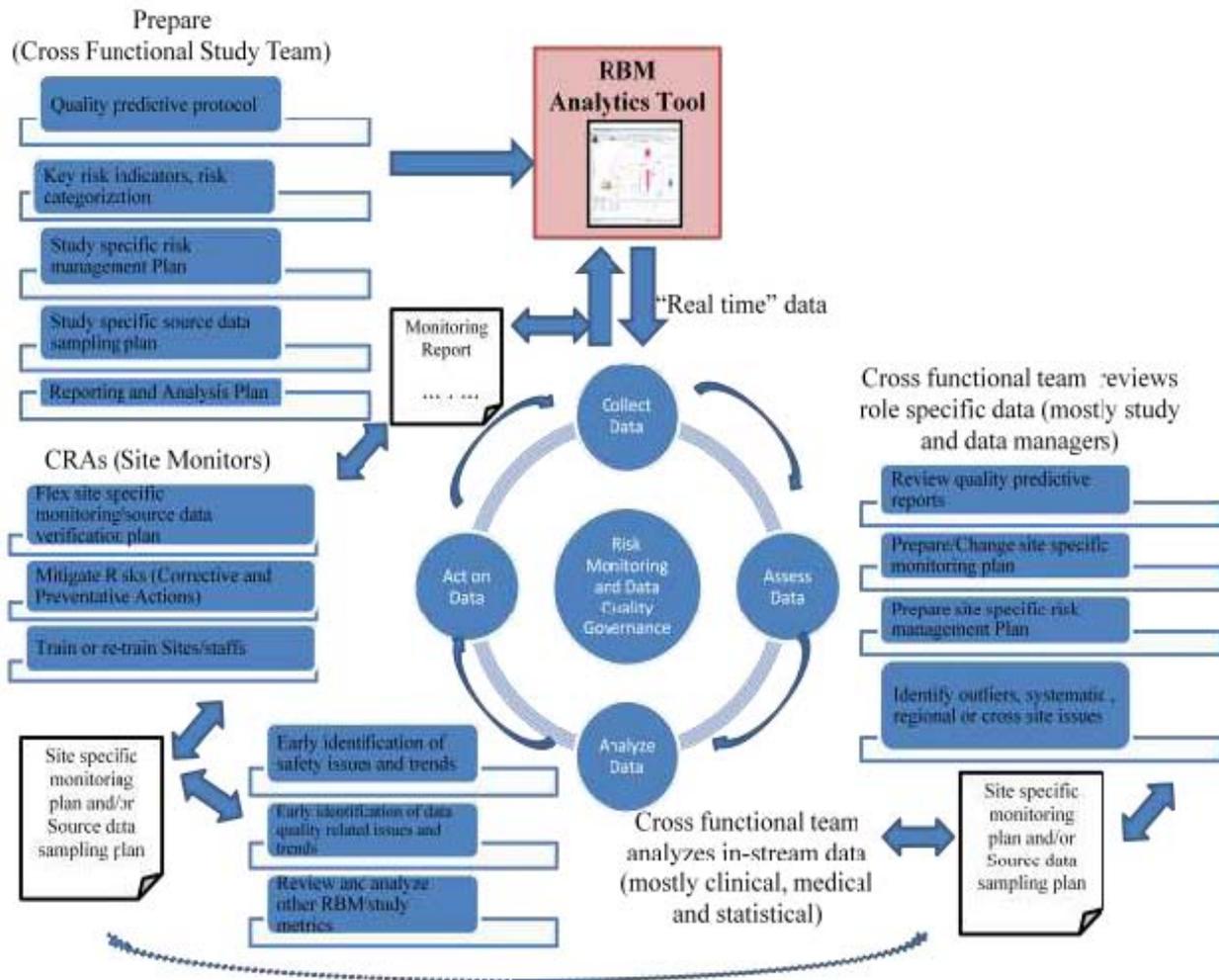
RBM and the associated technological infrastructure initiated at present are creating an opportunity to have the data available in-stream and for the appropriately qualified study team members to assess study, and center specific risks at each level of the data hierarchy for a more systematic governance of clinical study data (Figure 1). RBM related technological platforms are

also allowing for custom landing pages and enterprising the monitoring landscape. These platforms allows for a cross functional study team member e.g. clinical experts, medical experts, operational management experts and data management experts to have immediate visibility to center specific data as they are entered and related analytics, metrics and study performance dashboards. This type of a just-in-time centralized data visualization, surveillance, coupled with triggers and thresholds, allows for the interpretation and identification of areas of concern by the different subject matter experts. This, in turn, sanctions simultaneous mitigation creating an end-to end holistic data monitoring infrastructure. Therefore, the RBM ecosystem is facilitating fluidity to data monitoring leading to a more collaborative cross functional team-based data vigilance approach.

CHANGING ROLE OF THE STUDY TEAM MEMBERS

CLINICAL, MEDICAL AND STATISTICAL TEAM MEMBERS

Within the risk based landscape, the medical and clinical study team member's role is being re-defined and they are now designing fit-for-purpose predictive protocols based on upfront classification of critical data and study processes needed for multi-level risk identification. These types of predictive protocol, which go through peer review, help manage trial design related issues. The statistician is also being involved at the protocol design phase, so that the reporting and analysis plan could also be aligned with the critical data and adjusted for the identified risks. These scientifically and medically qualified study team members are proactively reviewing incoming data, identifying trends and triggers associated with the data and assessing the impact of errors on human subject protection and data integrity. The feedback received from the clinical team members allows for the clinical trial monitor to continuously shift their monitoring and source data verification strategies at a specific site. This focused central monitoring by the subject matter experts is presumed to expectantly lead to continuous mitigation of critical issues pertaining to human subject safety and data integrity. As a result, there is interdependence (Figure 1) undertaken between the clinical trial monitor and the study team members in driving the culture shift towards a more in-stream data visualization, review and quality governance.



DATA MANAGER

Similarly, data manager's role in the end to end study delivery has significantly broadened, which requires leading interactions with the monitoring team with conversations to translate the protocol into the case report forms; study specific monitoring plan, source data sampling plan and also with the technical team to translate the identified Key Risk Indicators (KRIs) into visuals. Data Managers are playing a more active role in centralized data analysis, trend and trigger identification. They are taking on a bit of the project management type focus on monitoring plan, source data verification and center specific monitoring sampling strategy. There also seems to be a greater overlap of roles between the data leader and the clinical trial monitor as they begin to identify the outlier sites, systematic, regional-cross site issues via the use of the in-stream informational analytics. The data managers in RBM are instrumental in designing the site specific source data sampling and monitoring activity plans based on the site specific triggers identified. RBM has shifted the role of a traditional Clinical Data Manager from a "data curator" to a very critical "information based" function which requires them to monitor and interpret the data in a routine fashion as they are received. The data managers are thus predicting study related

outcomes signals based on real time analysis of the risk indicators identified^[8]. In addition, data managers also are now engaged in the training of visuals technology and communicating findings and issues to the study team members and the monitors. Therefore, in the new RBM ecosystem, they are also performing a traditional monitor's task by reviewing data reported and analyzing the signals that might adversely impact the rights and safety of the clinical trial subjects.

OPERATIONAL OR STUDY MANAGER

In the same paradigm, a study or operational manager's role is also being redefined as they lead the study towards an integrated, convergent, holistic, just-in-time data monitoring and quality by design paradigm^[2]. Within this platform, the study manager is engaged from protocol design to study report generation. They are essential to ensuring that the study protocol is sliced and diced appropriately during the design phase to embed key risk indicators (KRIs) in regards to impact on patient safety and interpretation of results. Along with the establishment of predictive protocols, they are also assisting in designing operational plans that helps support an adaptive review and centralized monitoring of incoming data based on the risk assessment and supported analytics.

In addition, study managers are responsible to ensure appropriate analytics are in place to perform centralized review and just-in-time interpretation of study data. Within the risk based archetype, they are required to liaise with more stakeholders, are accountable in ensuring that all functional team members have reviewed the analytic ready data accordingly to their functional expertise; the risks are assessed, adjusted and mitigated to improve the probability of success. All in all, they play the role of the conductor in leveraging real time data review from numerous functions and applying the knowledge created to execute just-in-time decisions that improve trial efficiency and patient safety. They also play a key role in data review, trend analysis and trigger assessments. They are accountable for having continuous conversation with monitors on site and study specific risk indicators, targeting and tailoring the center specific monitoring plans on an ongoing basis and helping them flex the implementation of monitoring strategies at the center level through the course of the study. Therefore, in the new RBM ecosystem they are also performing a traditional monitor's task by ensuring incoming data as received is complete and the analyzing the signals that might adversely impact the rights and safety of the clinical trial subjects and quality of the data reported.

CLINICAL TRIAL MONITORS

Within the Risk Based Monitoring paradigm, the most significant change that a clinical trial monitor has to go through is behavioral. There needs to be adjustments by the clinical trial monitors in abandoning the traditional 100% source data verification^[9] psychology. They will need to re-educate themselves in risk based source document verification philosophy which is

based on targeted critical data driven sampling strategy. The most challenging aspect would be willing to shrug off the inherent perception associated with the “off-site” monitoring while still holding on to the merit of the in-person monitoring. The clinical trial monitors in the risk based monitoring environment are consistently utilizing risk indicators; risk assessment practices and tools for value driven discussions with their sites. They have to be technologically savvy to decipher the data visualization predictive tools to escalate risk-decisions identified and execution of corrective and preventative plan. The clinical trial monitors will have to rely on the assessment and analysis made by the cross functional study team members in driving their site specific monitoring strategies leading to a more engaged and collaborative monitoring overall. In addition, the clinical trial monitors must have the willingness to understand and adapt new technology and innovations as we move more and more towards cloud based architecture, electronic document collaboration, and centralized content repositories. This type of shared data monitoring throughout the life of a study will aid in the delivery of effective risk based quality governance framework and lead to the changing face of the monitor in the future. As technology becomes the mainframe of monitoring, a clinical trial monitor may evolve to be someone with not only scientific and clinical expertise but someone with combination of these and the technological expertise.

These affirmative changes in the real time monitoring archetype, comes with its own challenges. Some of the current challenges are highlighted below.

- Streamlining the training and understanding of risk based monitoring among all stakeholders including clinical research sites
- Implementing behavioral and skill related change management system
- Effective and consistent utilization of risk indicators; risk assessment practices and tools by different cross functional team members
- Appropriately implementing RBM model in a global landscape
- Continuously evaluating and re-defining the model and implementation strategies

In conclusion, conventional monitoring was based mostly on data reviewed in silos by the monitors. RBM is bringing a paradigm shift from the conventional means^[9]. This will need coordinated, focused and streamlined efforts to be successful, leading to a team based approach [10], [11]

Risk Based Monitoring is creating interdependency in data monitoring and quality governance framework. A monitor no longer seems to be a single entity, but a group of people from cross functional teams that share a joint accountability. However, the adoption of the risk based principles and the quality governance framework is still at its infancy and will need to go through the behavioral and technical adjustments in the years to come before it hits its maturation. All

stakeholders in the clinical research environment will not only need to be aware, educated and trained, but also willing to change, re-train and adapt, and then we may be able to see improved safety and quality in clinical trial outcomes overall.

DECLARATION OF CONFLICTING INTERESTS

The Author(s) declare(s) that there is no conflict of interest.

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CREDITS

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