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

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ABSTRACT

A Risk Based Approach to Monitoring (RBM) guidance released by the EMA and FDA has generated tremendous opportunities and discussions on the prospects of clinical trial monitoring practices. This guidance has raised an array of new tools, technologies and systems to facilitate the approach. However, there is very limited information on the how the clinical trial professionals will have to adapt and adopt their behaviors, skills, competencies and knowledge to leverage the optimal outcome. This paper via literature search and dialogue sessions explores the current working practices and illustrates the evolving role of a clinical trial monitor and key study team members in the RBM landscape. The current working practices suggest that RBM is creating interdependencies between the cross functional team members. This interdependency and appropriate leveraging of the competencies between the study team members is a key component to driving the culture shift towards a more in-stream data visualization, review and quality governance.

KEYWORDS

Risk Based Monitoring, Clinical Trial Monitoring, Clinical Trial Monitor and Quality Governance

INTRODUCTION

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 study is conducted in compliance with the applicable regulations, SOPs and study documents (E6 Good Clinical Practice, 1996). Before the advent of RBM and associated technological interfaces, a monitor was typically engaged in the review of individual subject related data points embedded in the case report forms (CRFs). In the traditional setting, frequent on-site monitoring with 100% source data verification had been deemed as the “gold standard” for meeting regulatory

obligations (CTTI, 2012; Cognizant, 2012).Through these on-site monitoring visits the clinical trial monitor has been assessing and reporting non-compliance, data related errors and trends at sites via on-site monitoring of 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. These assessments were 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 correlation between these challenges and the fact that over the last several years, the types and nature of deficiencies identified through regulatory inspections have not changed (FDA Risk Based Approach to Monitoring, 2013). 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 Japan PFSB) and TransCelerate's initiative (TransCelerate, 2012) have contributed to the evolving concept of RBM by providing guidance (CTTI, 2013; FDA Risk Based Approach to Monitoring, 2013 ; EMA reflection paper, 2013; PFSB, 2014) 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)* makes clear that sponsors can use a variety of approaches to managing data quality through technology enabled data driven actions by targeting monitoring activities where they will deliver the best benefit to the study and patients *(*FDA Risk Based Approach to Monitoring, 2013). 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. Even though RBM is at its infancy, per Transcelerate Biopharm there are currently 54 active RBM trials (Phase I-IV) that have commenced utilizing the TransCelerate methodology across 10 sponsors.

RBM and the associated technological infrastructure is creating an opportunity to have 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 quality 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, medical, operational, monitoring and data management experts to have immediate visibility to center specific data in real time including related analytics, metrics and study performance dashboards. This type of just in time centralized data visualization and surveillance, coupled with triggers and thresholds allows for interpretation and identification of areas of concerns by the different subject matter experts. This in turn sanctions simultaneous mitigation creating an end-to end holistic data monitoring infrastructure. Therefore, it is critical to understand how the functional study team members are leveraging the RBM tools and technology to facilitate fluidity in overall data monitoring leading to a more collaborative cross functional team based data vigilance approach.

CLINICAL, MEDICAL AND STATISTICAL TEAM

Within the risk based landscape the medical and clinical study team member's role is being re-defined. 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 protocols which go through peer review help manage trial design related issues. The Statistician is also 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 risks identified. 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 site 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 lead to continuous mitigation of critical issues pertaining to human subject safety and data integrity. As a result, there is interdependence (Figure 1) between the clinical trial monitor and the study team members driving the culture shift towards a more in-stream data visualization, review and quality governance.

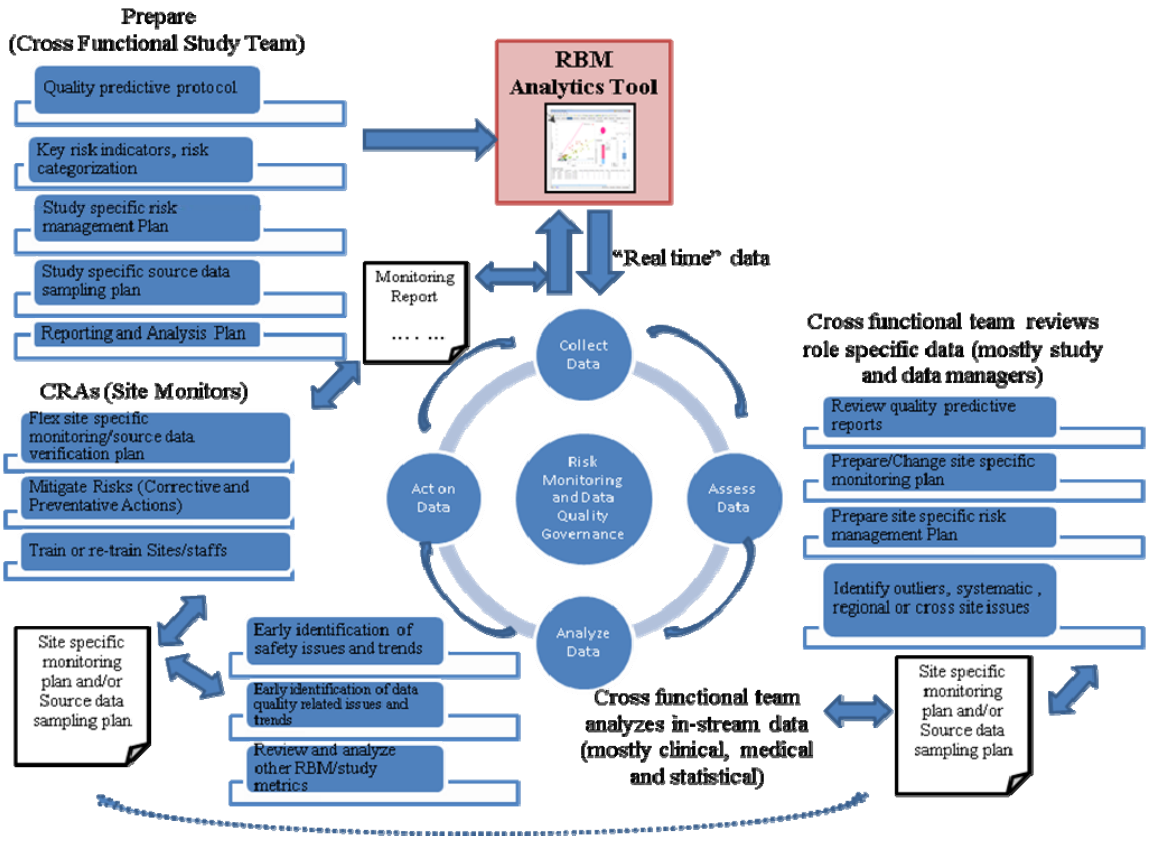

Figure 1: Cross functional study team members and their involvement in the RBM model and data quality governance

DATA MANAGEMENT TEAM

Similarly, the data manager's role in the end to end study delivery has significantly broadened. This now requires leading interactions with the monitoring team to translate the protocol into the case report forms; a study specific monitoring plan, source data sampling plan and–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 project management type focus on a monitoring plan, source data verification and center specific monitoring sampling strategy. There is a greater overlap of roles between the data leader and the site monitor as they begin to identify the outlier sites and systematic, regional-cross site issues via the use of the in-stream informational analytics. The data managers 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" role to a very critical "information based" role which requires them to monitor and interpret the data in 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 (Quintiles, 2014). 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. 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 MANAGEMENT TEAM

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 (CTTI, 2012). 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) with regards to impact on patient safety and interpretation of results. Along with establishment of predictive protocols, they are also assisting in designing operational plans that helps support 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 according 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. In the new RBM ecosystem they are also performing a traditional monitor's task by ensuring incoming data as reported 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.

SITE MONITORING TEAM

The most important change for site monitors is behavioral. There are required behavioral adjustments needed by the clinical trial site monitors in abandoning the traditional 100% source data verification (Morrison et al., 2011) psychology. They will need to re-educate themselves in the risk based source document verification philosophy which is based on targeted critical data driven sampling strategy. The most challenging aspect is likely their willingness 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 site 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 site monitors must 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 site monitors must understand and adapt new technology and innovations as we move towards a 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 be someone with not only scientific and clinical expertise but with a 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 a 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 on data review by the monitors. RBM is a paradigm shift from the conventional means (Morrison et al., 2011). Efficient execution of RBM will need a team based coordinated, focused and streamlined approach to be successful, (Kumar et al., 2014; Stokols et al., 2008). Risk Based Monitoring is creating interdependency in data monitoring and quality governance. A monitor is no longer a single entity but a group of people from cross functional teams that share joint accountability. However, the adoption of the risk based principles and the quality governance framework is still in its infancy and will need to go through the behavioral and technical adjustments in years to come before maturation. All stakeholders in the clinical research environment not only need to be aware, educated and trained but also willing to change, re-train and adapt. Then we will see improved safety and quality in clinical trial outcomes.

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