

Risk Based Monitoring—Current Challenges with Implementation

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Abstract

Background: The FDA issued guidance for the industry on the “Oversight of Clinical Investigations-A Risk-Based Approach to Monitoring (RBM however the guidance lacks specificity on what successful implementation should look like and strategies that will address global adoption.

Purpose: To address current challenges with implementation of risk based approach to monitoring in the global research platform and suggest potential solutions.

Methods: Literature search was conducted followed by several discussion and brain storming sessions conducted to arrive at this brief write up.

Conclusions: Having a team science approach to implementation of the risk based approach to monitoring at the initial stage to ensure effective and efficient adoption across the industry in the global platform. This will eliminate inconsistencies in understanding as well as implementation of RBM by the investigational research sites.

The stakeholders involved in the conduct and control of clinical trials are constantly aiming to reduce the complexity of clinical trials; accelerate patient recruitment and reduce overall cost involved. Recently, the U.S. Food and Drug Administration (FDA) issued guidance on “oversight of clinical investigations-a risk-based approach to monitoring [1].” This guidance has generated a keen interest among the sponsors and clinical trial sites about its implications and adaptability. This risk based monitoring (RBM) approach is intended to improve the trial data integrity and safety of the participants involved, by focusing sponsor oversight on the most important aspects of study conduct and reporting. The regulatory agencies are expecting the sponsors to modify current focused on-site monitoring approach to a RBM model, which utilizes a combination of centralized and on-site monitoring techniques to improve real time decision-making leading to overall efficiency of clinical trials as it pertains to patient safety and data quality. This approach is speculated to reduce the trial costs by as much as 15-20% [2]. The FDA guidance makes 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. In stream review of the data will help drive the pre-determined risk measures for the study, and will help sponsors in visualizing comparative risk indicators across all sites. It is believed that these site specific indicators and risk metrics will be able to overcome inadequate monitoring and failure by monitors to bring investigational sites to compliance. Also, the technologies and digitization of clinical research data will supposedly allow sponsors to scrutinize and target sites that are projected to be riskier based on their individual metrics.

Currently, there is no universally agreed specific definition for RBM at present. RBM is considered a flexible approach on clinical trial monitoring, which includes a mix of centralized and on-site monitoring practices tailored to a specific study based on the pre-identified risk indicators represented by each site and calls for monitoring focus on activities and data, which could have

the most potential to impact patient safety and data quality.

Risk-based monitoring is not a one-size-fits-all approach. RBM practices that will be established by sponsor companies will be at a global level and each sponsor might tailor the RBM strategies a bit differently. Clinical research sites work with multiple sponsors and conduct multiple studies and might have to adapt themselves to various RBM strategies and expectations. High complexity, high risk, large or geographically widespread studies may need a different approach than a lower complexity and low risk trial. There is a need for ensuring that clinical research sites are equal partners in the discussions regarding RBM models and strategies.

While this transformation takes place, it is imperative to recognize the perception of the sponsors, investigators, and their staff, on this new concept and their preparedness to adopt it. Additionally, the potential merits and de-merits of RBM may in fact be quite varied between geographical regions globally, depending on the existing infrastructure, training needs, resource availability, and most important, the culture and mindset of the work-force involved. These variables and the changing role of the clinical trial investigators (stringent and emerging new regulations, trial intricacies, integration of IT solutions, recruitment challenges etc.) makes it truly worthwhile to understand the gaps and needs as we find today.

The Impact of FDA and European Medicines Agency (EMA) [1, 3] guidelines so far has been a mix of hope and despair. Some experts feel that the RBM approach would bring a paradigm shift in clinical trials, however the guidance lacks specificity e.g. how to assess risk, measure types of risks and which situations are pertinent for RBM, etc. Also there is a need to get a clear directive from these agencies on how to use the cutting-edge technology efficiently and effectively to comply with the guidance. There is a lack of strategic plan to improve centralized oversight to adopt this RBM at investigational sites. The regulators are expecting the industry to innovate technology, business processes and

conducive practices for implementing RBM. If this approach is not consistent across the industry in the global platform then this could lead to inconsistencies in understanding as well as implementation of RBM, at least at the initial stages.

There are several barriers to implementation of the RBM at organizational, operational, and technical levels at present. Organizational barriers could be challenges in managing international investigational sites; most of these trials are managed by CROs (Contract Research Organizations), which have their own systems and data standards. Also, most of these sites have limited resource, infrastructure and technical assets and depend considerably on the face time with the sponsors to keep the momentum of the study. The real difficulty would be standardizing the approach in compiling the data, ensuring appropriate resource at sites to have data entered in an expeditious fashion, which ultimately could be analyzed in the real-time using the centralized monitoring system. Other factors could be depending on the experience of the sites involved in a study, the sponsor might not have enough historical data to generate site specific risk indicators which is essential in designing the RBM model for the sites. Furthermore, clinical trial type, therapeutic area, site selection and stage of trials add to this complexity. At the operational level depending on the country and local regulations there is still resistance to move from source data verification (SDV) to source data review (SDR), as they anticipate that regulators may find this as an oversight issue which could ultimately delay the drug approval process. There is not much evidence of success for this model at a small and larger level and the work force is not trained to face this sea of change. Technically, some of the companies may not have the Electronic Data Capture (EDC) system to capture clinical biometric data, and may still be using hard copies to document and review outcomes. In addition, sites might not have the required technical infrastructure or knowledge to support the RBM approach to monitoring. This demands a centralized weighted

monitoring system which will provide a mechanism for a signal to emerge from the collected data which could not have been discovered through SDV on site.

In order to optimize RBM adaptability the stakeholders need to work on the “*Team Science*” principles. All of the stakeholders’ e.g. clinical experts, technical experts, data management professionals, clinical operations team, consultants, senior management and most importantly regulators should work in cohesion to successfully implement RBM. An integral part of this would be to continuously educate, train and provide support to the staff involved into data collection during all phases of RBM implementation.

There are inherent challenges and issues in execution of investigational clinical trials as shift to RBM approach continues from more affluent regions of the world, towards the emerging markets. At present there is a gap in understanding if the investigational sites at a global level will be able to support the RBM practices and the needed technological infrastructure. Moreover, differences in standard of care may need to be taken into consideration when applying the RBM models in developed versus emerging markets. To ensure adequate adoption by the research sites at a global level, it is critical that the industry validates the perspective of clinical research sites on the proposed merits of RBM and readiness of investigational sites globally to adopt and support RBM practices.

In conclusion, if we need to improve human health by developing new and effective treatments, we need to ensure that the safety of the patient is paramount. To do so, we need to move very strategically and steadily to adopt RBM. Also, as a part of this team effort, a web based portal for the stakeholders to communicate if they are not certain how to proceed or just for sharing their views and experiences would be a great move. An integrated team science approach is needed to effectively implement this very promising innovative method to improve patient safety and clinical trial data quality.

Declaration of conflicting interests

The Authors declare that there is no conflict of interest.

Declaration of Funding/Grant

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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