

Review Article

Evolving risk based monitoring scenario and change management associated with it

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ABSTRACT

Clinical research and drug development is evolving continuously resulting in pharma companies looking for newer ways of getting drugs faster to the market. Managing clinical costs and coping with major regulatory hurdles poses challenges of finding ways to do more with a small budget. The Food and Drug Administration (FDA) guidance for industry on “risk based approach to monitoring”, TransCelerate Biopharma INCs “risk based monitoring methodology position paper” provides guidance, recommendations and methodologies for conducting risk based monitoring (RBM). However, limited experience in the implementation of these methodologies poses questions on practical challenges that pharmaceutical companies are either already facing or will face during the implementation of these recommendations. This paper describes the evolution of RBM strategies and discusses the complexities that clinical research organizations (CROs) and service providers could face while implementing RBM. This paper also suggests how pharma companies may have to adapt their organization to this new model by highlighting changes in roles and responsibilities of relevant stakeholders including site investigators, site monitors and lead data managers. A few suggestions for ensuring smooth change management have also been proposed for each stakeholder.

Keywords: Risk based monitoring, Change management, Clinical project managers, Site monitoring, Recommendations for successful implementation / dealing with change, Lead data managers

INTRODUCTION

Pharmaceutical companies today face a double edged sword while looking to conduct complex global trials. While having timely patient recruitment, managing the overall trial costs and finding solutions to regulatory roadblocks that potentially impact approval timelines, pharma companies also need to ensure that patient safety, data quality and trial integrity are not jeopardized.

In August 2013, the FDA published its final guidance on risk based approach to monitoring which reiterated main points of draft published in 2011. It was aimed at encouraging pharma companies to consider some changes to their traditional monitoring methods while meeting the

regulatory and statutory requirement.^{1,2} In May 2013, TransCelerate Biopharma INC also published its position paper on RBM proposing a standard approach for RBM that could be adopted by trials irrespective of their stage and phase (phase 1 through phase 4).³ Setting the stage, was a paper published by the European Medical Agency (EMA) in August 2011 on developing a more systematic approach helping prioritization of risks associated with trials and ensuring that good clinical practices are followed.⁴

Though the complete and effective implementation of RBM methodology seems a daunting task today, the industry is taking slow but sure steps towards the realization of this goal. A shift in outlook can be seen in

pharma companies as well as service providers. Organizational goals and governance structures are being revamped to accommodate and build strategies for effective implementation. The service providers are eager to tap the huge market that RBM can offer and use it for their own growth. To achieve this, they are developing technology and process solutions aimed at helping the pharma companies in realization of their objectives.

These changes in outlook of major stakeholders have led to the gradual evolution of RBM in a short time frame. While advancements are being made, complexities and challenges in implementation of RBM continue to exist and some of these are discussed below.

Complexities of implementing RBM

In absence of any defined set of rules for implementing RBM methodology and reduced visibility to its implementation results-many questions are left unanswered. Some of the complexities and challenges that pharma companies and CROs are facing are cited below.

The identification and selection of a well-established service provider

With multiple options available, pharma companies struggle to make a choice for suitable partnership. The service offerings are various but not supported by any success stories yet. While some providers claim strong history of technology background (with in house analytics and visualization capabilities) they may lack experience in clinical operations services. In contrast, a CRO with strong domain expertise would lack technology for building data factory that would accommodate multiple data sources- a roadblock for analytics model. In a scenario where pharma companies may have to outsource different activities to multiple partners, it might pose governance challenges while managing internal change management.

Driving change management within their own organizations

Resistance from internal stakeholders is one of the major challenge pharma companies have to deal while trying to bridge the gap between traditional and adaptive monitoring. Considering the nascent nature of the RBM model, it needs to be realized that a change of this magnitude will need a focused and continuous communication flow across teams.

Need for change seen in CROs and service providers

While pharma companies are dealing with challenges as discussed above, there is similar pressure on CROs and service providers to continuously revamp their outlook. CROs, weak in technology are considering partnerships with information technology (IT) companies. Tie ups

between tech-empowered organizations and research organizations are seen aimed at offering a complete package to sponsors.

With challenges existing, what is needed is a roadmap that defines some prerequisites that would be needed for effective implementation from people, process and technological aspects. Some of these are discussed below:

Pre requisites for implementation of RBM model

Before embarking on implementing RBM across projects, a check needs to be performed on availability of certain parameters that would translate to success factors. Of utmost importance will be professionals who have performed centralized data review and understand the concepts related to same. Clinical data managers and onsite monitors could be repurposed for central review based on their remote data review experience. Clinical analysts who define the algorithms for signal detections and predictive analytics will play a major role in trend analysis and Trigger managements. Clinical project managers who can drive discussions with multiple stakeholders in risk assessment meetings will be pivotal. They will be involved in ongoing risk review and update to integrated quality risk management plan for implementing adaptive monitoring to sites based on their risk profiling.

With changes in profiles as discussed above, a change in process from traditional methodology will also need to be defined. For pharma looking to adapt the trials in RBM delivery model, will need to focus on updating or creating new relevant templates e.g. project plans, risk management plans etc. Project Plans would need to factor additional tasks in study start up, conduct and close out sections. For e.g. timelines for tSDV configuration could be added to study build activities. Standard work operating procedures may need to be developed / revamped to include the changes in working practices for departments like data management and medical data reviewers. With evolving roles and responsibilities of the major stakeholders, the governance plan clearly defining the communication and escalation pathways will also need to be re visited.

Technology being core to implementing the RBM, it becomes an integral part of the overall operational plan. To ensure that maximum benefits are derived, pharma companies will need to have access to technology that can integrate data from multiple sources and has capability to standardize the same. Technology / tool that will enable near real time review of the study risk and driving go No go decisions via a customizable visualization and Analytics tool, would be ideal.

Few organizations may have internal capabilities as discussed above or are piloting trials in the RBM model using various services available in market- however majority others seem skeptical. Companies seem to wait

for results of success stories before venturing in new territory of RBM. With prerequisites discussed above, roles of some primary stakeholders including site investigators, site monitors and lead data manager will undergo significant change. Challenges associated while dealing with this change management will be discussed below. Few recommendations for overcoming these challenges are also cited for each stakeholder.

Role repurposing for major stakeholders and challenges associated with same

I - Site investigator

For effective implementation of RBM, reduced or targeted source data verification (SDV) will be essential. However this would imply reduce onsite time with site investigators and site coordinators. The dynamics of changed working pattern and decreased face to face interaction could result in resistance at sites for below mentioned expectations.

Enhanced adherence to data entry turnaround time as per contractual agreement

Faster data flows across teams for speedy data base locks will require stringent adherence of sites to data entry timelines. This could lead to building pressure on sites for better compliance to DE when compared to traditional environment where milestones (interim and final database locks) drove the urgent need for data cleaning and review.

Increased focus on the quality driving expectation for self QC at sites

With monitors performing source data review (not just 100% SDV) and monitoring for only critical data points, there will be higher accountability on sites for efficient data transcription. Sites will thus need to adhere to stringent quality control procedures for better compliance and minimum findings during monitoring visits.

Centralized data review would help in identification of issues related to critical data points in a reduced SDV environment, however access to source data can be impeding factor especially for cases of missed safety data reporting resulting in risk seepage. Subsequently, it could influence major decisions for a study. It seems imperative for sites adopt self QC as a practice while working in RBM model.

Change in the modalities of interaction: from face to face to web based

Reduced onsite monitoring combined with required remote contacts with central monitors is the key to effective monitoring based on risk profiling of sites. Interactions between sites and monitors will be more virtual- leveraging the technological advances. Face to

face communications will be replaced by regular telephone contacts, web ex and video conferences. Sites and Monitors will need to drop the preference for personal interactions which will need major change management exercise. Sites will need to drive better compliance, will need to be proactive and better prepared in identifying issues for discussions with central monitor and site monitors. Site performance metrics (e.g. number of missing pages, pending queries for action) will become the benchmark for sites inclusion in future trials.

To effectively manage the challenges as discussed above, few recommendations have been suggested.

Recommendations for dealing with change

- Sites will need to understand the rationale behind RBM model and have transparent productive discussions with sponsors for any roadblocks anticipated.
- Sites will need to be open minded regarding expectations and need related to better compliance to DE and query TAT, self QC etc. driving sites performance metrics.
- Sponsor should initiate better incentives for sites managing change effectively.
- Sponsor to set up counselling counters for sites facing challenges and providing support via training till sites are mature.
- Conduct regular feedbacks / surveys to understand improvement areas / support needed.

II- Site monitors

Data today is more integrated, easier to access ("at your fingertips"), cloud-based, mobile and tablet-accessible. The bridge between pharma and IT has been established. With these advancements, role of site monitor has undergone major uplift resulting in challenges. Few are discussed below.

The implementation of adaptive monitoring

Adaptive monitoring will replace traditional monitoring and role of Site monitor will extend from identifying transcription errors to more focused review aimed at mitigating likely sources of error and identifying the inherent risks at site, based on trend analysis. With this extension of responsibilities, new expectations will need to be met. Monitors will need to train themselves for targeted source data verification (tSDV) and its implementation. Trend reviews and observations made during onsite visits will drive need for monitoring frequency updates and adjustments to monitoring plans.

Actioning of triggers as added responsibility and adherence to TAT

The risks identified for a study protocol during risk assessment meeting are tracked as function of risk

indicators. These risks are tracked as system generated alerts called Triggers when thresholds for risk indicators are met. Each trigger requires an action to ensure risks are reviewed and corrected. Site monitors will have *additional responsibility* of actioning these triggers as defined in the monitoring action plan / by the in-house monitor. Since the focus will be on implementing corrective or preventive action in near real time, monitors will have to adhere stringently to timelines for actioning the triggers.

Multiple communication touch points

With remote calls and remote visits taking precedence in working pattern, communications with stakeholders including central monitors and/or remote monitors, sites will demand greater involvement of site monitors in understanding ongoing / pending issues at sites. Contacts being more virtual – building a rapport in initial stages of study and introducing dynamism in working style will be the key. Monitors will also need to be data driven, milestone oriented and demonstrating strong leadership skills. With sites undergoing change management, monitors may experience hostile environment and would need to have positive approach while dealing with multiple stakeholders.

Site performance an indicative metrics for site monitors performance

Non-compliant sites, poor site performance as indicated by increased cases of protocol deviations, issues observed during source data review (SDR) could be a direct reflection of site performance and an indirect reflector of its monitor's performance. With emphasis more on performance tracking, site monitors could face the heat and inability to adapt could result in affecting overall trial performance.

Recommendations for dealing with change

- Interactive workshops for dealing with change management.
- Rewards and recognition for monitors successfully implementing RBM model and sharing success stories within organization to drive acceptance across.

Lead data manager

At site front with roles of site monitors and site investigators undergoing change, a role that will also experience paradigm shift in remote set up is that of the lead data manager (LDM). Some of the additional responsibilities and changes in the working pattern that could be observed are discussed below.

Functioning in centralized data review environment

Lead data manager will need to identify critical data points during risk assessment meeting and build relevant study plans for mitigating defined risks. Traditionally edit checks and listings defined in data management plan were used for data cleaning, but in RBM model the LDM would need to assess the feasibility of adding an automated trigger for near real time identification of risks. Timely discussions with the clinical team for identified outliers could be of more value rather than waiting for query resolutions and related discussions.

Defining streamlined data cleaning strategies for faster data flow

Traditional data cleaning activities were milestone driven (often linked to interim and database locks). In RBM model, demand is for quicker data flow and availability of clean data within defined timelines post visit occurrence. This would require LDMs to drive change management within team related to data cleaning pace while keeping members motivated to adapt to new expectations. The LDM would need to conduct regular sessions with team for finding ways of working faster with accuracy. Data flow monitoring will involve LDMs to oversee some additional metrics to ensure the current and downstream activities are in line with expectations. Few examples of additional metrics to review include

- Time for DE post visit occurrence
- Time for data cleaning post DE completion
- Timelines for data flow to next level of review, if needed
- Data analytics review

The adoption of newer tools and technology for data cleaning

Evolution in technology led to evolution of data cleaning activities. Transition from paper based to Electronic data capture (EDC) resulted in near real time cleaning. SAS checks have decreased the extent of manual review that was performed earlier. LDMs may be expected to use tools that would drive need for faster data cleaning and flow across levels. Using these tools the LDM could identify the potential backlogs of queries and missing pages at site, pending coding or vendor queries etc. and take needed steps for quicker cleaning.

Few examples of some tools that LDM may have to use in day to day activity.

- A tool for the identification and prioritization of data that should be ready for review.
- A tool for the quick and easy review of data using data visualization technologies like Spotfire Tools for data Analytics.

Recommendations for dealing with change

- Effective and pro-active communication from the leadership to study teams selected for studies that will be delivered in an RBM environment.
- Practical aspects of differences between traditional versus RBM model. Knowing the differences will help teams in getting a clear understanding of RBM model.
- Setting up trainings and providing team's suitable time to understand the new model, associated tools and technologies.
- Rewards and recognitions to the pioneers involved in the implementation of RBM studies to drive a positive mindset towards this model.

CONCLUSION

Thus we see that RBM is evolving rapidly with pharmaceutical companies taking cognizance of the need for implementation of this new strategy, aimed at reducing costs, pre-identification of risks, driving the optimal usage of resources while focusing on quality, and leveraging the optimal usage of technology for getting drugs faster in the market. If complexities associated with the implementation of RBM can be understood earlier, it would help in defining methods focused on finding solutions. Trials thus could be managed more cost effectively, could be more adaptive and could be more focused on risk mitigation by using triggers highlighting real time issues. With this evolution it was necessary to discuss what has changed and what will be new responsibilities of the key stakeholders. The paper highlighted these changes for three stakeholders including site investigators, site monitors and lead data managers. Changes are not easy to implement and can lead to resistance from teams thus jeopardizing the achievement of organizational goals. In view of the same, along with the changes that each stakeholder will experience, we have attempted to discuss a few

recommendations as well that could be helpful in driving change management effectively.

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