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Review Article

Transformation in site monitoring practices through risk based monitoring

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ABSTRACT

As the current trends in clinical trial industry, is evolving day by day and adopting upcoming technology to integrate data from different sources into risked based monitoring (RBM) Portal, to increase efficient tracking system in a way that help in understanding site characteristic and make on-site monitoring visit more focused and accurate. Transformation from traditional monitoring method to RBM solution will significantly improve quality of data and will also reduce study risk and time. RBM is a standardized, systematic approach to identify and assess potential risk.

Keywords: Risk based monitoring, Adaptive monitoring, Triggered monitoring

INTRODUCTION

As the industry implementation of risk based monitoring (RBM) model progresses, one area to receive more focus than other has been the site monitoring visit (SMV) or routine monitoring visit (RMV), how it needs to evolve as the clinical quality oversight model changes, and what this implies for on-site monitors and remote monitors. Conventional on-site monitoring visits and site management practices are governed by a clinical study monitoring plan (CSMP). In broad terms the plan describes on-site monitoring and management with fixed frequency of monitoring (depending on trial indication, study population, complexity, submission timelines, scope and budget) with the basic conditions of when an urgent intervention or on-site oversight is required. In more advanced examples a specific description of data points for On-Site review and pointers for discussion during face-to-face contacts are included. The RBM approach not only reduce on-site monitoring significantly however it make an on-site visit more focused and an accurate visit. Additionally TransCelerate's framework for RBM has helped in differentiating the value of source data verification (SDV) and source data review (SDR). While the former is essentially data transcription quality checks; the latter is review of the origin of the information and therefore the processes related to it. SDV in the new approach is targeted based on risk planning and adapted through the study as the risk profile of the site or protocol changes rather than executed for 100% of data till last monitoring visit, or at some arbitrary fixed percentage of data points.

In this paper I discuss the realignment of processes and roles, and adoption of software technologies that require serious consideration when organizations consider implementing RBM and that the role of the on-site monitor may be transformed in positive ways for both sites and the monitors themselves. Paradoxically the groups often not engaged in the impact of RBM are the sites and monitoring community and hence it is befitting to elaborate on how important their future role is going to be. For the purpose of this article and so that core clinical operation members can more easily relate to this on-site monitoring visit processes and activities have been traditionally classified as those that precede an on-site monitoring visit (preparation), during on-site monitoring visit (conduct) and post-monitoring visit (follow-up).[1-7]

ON-SITE MONITORING VISIT PROCESSES

Before introducing and implementing RBM in monitoring methods, on-site monitors need to follow a fixed periodic frequency to conduct an on-site monitoring visit. This frequency was planned and documented at the beginning of the study, the most common frequency followed by most of the pharmaceutical companies is 4-6 weekly visit.[7,8,11-13]

As the industry adopts risk-based approaches of monitoring, it is becoming evident that some of the processes and activities which were once handled by on-site monitors will be shared by remote or central monitors. Though there is a view that the scope and value of on-site monitoring activities would tend to be reduced in this model, I contend here that the role of an on-site monitor will shape up to be more enriching and more efficient.[7,8,11-13]

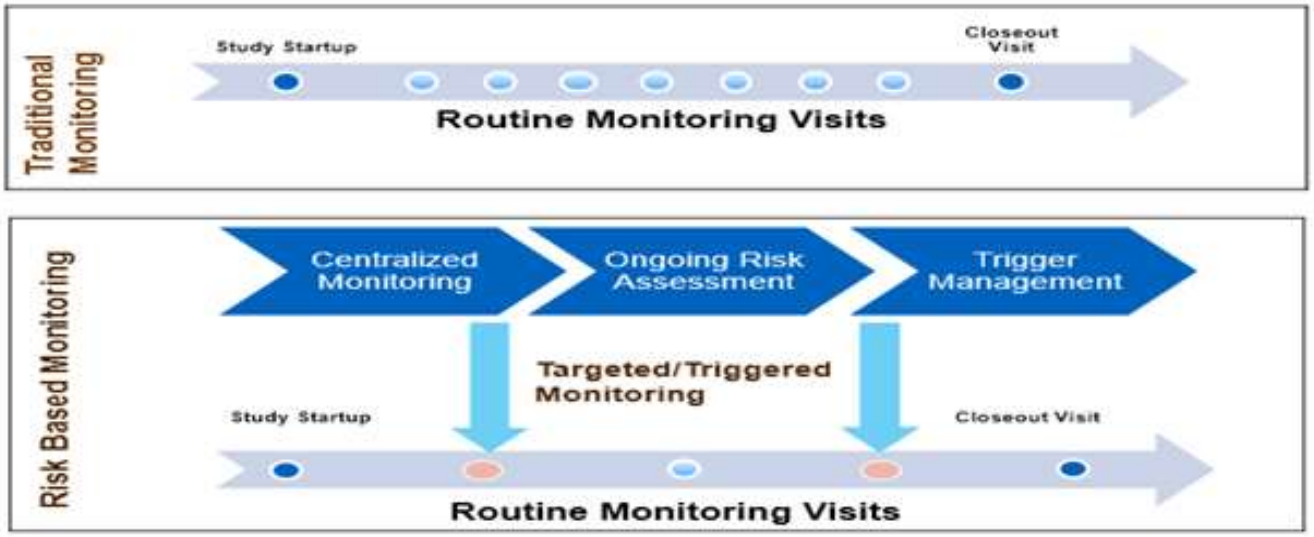

Figure 1: Comparison between traditional monitoring and risk based monitoring.

PRIOR TO MONITORING VISIT (PREPARATION PHASE)

Traditional way of preparing on-site visit involve review of past monitoring visit reports & follow-up letters, current enrollment status of the site, data entry status, investigator/trial master file, IP accountability status, query load, SDV backlog at the site and many more. In traditional way on-site monitor need to download reports using various system/tools (IWRS, eCRF etc.) and then analyze all reports for the preparation of upcoming monitoring visit. This is a time consuming effort which also require a lot of manual review/activity and which may became more crucial where an on-site monitoring required at short notice.[14,15]

The age-old practice of scheduling a routine SMV or an ad-hoc SMVs at short notice, resulting in sub-optimal preparation, will change. In the new world, there will be greater rationalization of on-site monitoring visits based on risk assessment and risk scoring. The requirement to perform or not perform a SMV will be objective and based on scientific and ethical principles. On an ongoing basis there will be insights compiled by remote or central monitors based on their analysis of data which will be available to on-site monitors to review. The results of such analysis could vary from tactical review of site performance to subject level review to surveillance using trends and signals in the data. Hence, the expectation from a monitor on an ongoing basis and also before a SMV is a comprehensive understanding of safety risks or issues with trial subjects as well as areas of focus for quality enhancement at the site. The on-site monitor will be focused on high value activities and is relieved of the significant burden of doing comprehensive verification of data that conventionally led to inconsistent performance due to numerous variables such as monitor experience and their ability and capability for detailed QC work, as well as simply the time remaining after dealing with other issues at site.[14,15]

RBM enablement modified monitoring visit preparation

The on-site monitor will be responsible for keeping track of key performance indicators (KPIs) and key risk indicators (KRIs) that can focus support and investigative efforts during an onsite visit. Applications that can aggregate and analyze data and from there generate reports and alerts can provide the logical path from the IQRMP to the critical variables and KPIs & KRIs that could potentially impact the scientific outcome of the study.[1-7]

For implementing RBM technology and services industry need to use or develop their local integrated warehouse, a statistical model and a communication platform/portal.

With the help of latest technology and advancement of RBM solution, central monitor or remote monitor will

prepare a central review report based on the alert and data monitored during central review, central monitor will share central review report with on-site monitor during preparatory phase of his visit. Central review report will cover and highlight active observations, pending action item for site/on-site monitor, SDV target etc. {Dashboard used for RBM should have capability to generate central review report within the portal an should be visible to all applicable stakeholders.[1-7]

This process of RBM and central review will reduce a significant amount of time and effort taken by on-site monitor for preparing an onsite visit. Preparation will be done by RBM team utilizing statistical analysis of whole data coming from different CTMS systems.[3,4,6]

DURING ON-SITE MONITORING VISIT (CONDUCT PHASE)

In the RBM model, efforts required during an on-site monitoring visit will be dependent on the insights and performance of a site from a quality and risk perspective. In an ideal state, the monitor should perform the following:

Utilize the insights and report provided from remote or in-house review

1. Perform the level (percentage) of SDV specified in the IQRMP based on assessed risks.

2. The focus of monitoring will shift from SDV to evaluating processes followed at the site for study conduct. Some of the key items include (but not limited to):

i. Relationship management with primary investigator and study staff.

ii. Understanding the subject pathway during the conduct of the study and assessing logical checks to what is being recorded in source documents.

iii. Ensuring appropriate study procedure execution and investigational product handling is in place per site responsibilities.

iv. Alignment or compliance of site activities with their institutional procedures and best practices.

v. Assessment of site staff understanding their specific responsibilities & competency reviews.

vi. Root-cause analysis in areas where there are significant issues and development of remediation plans and corrective actions.

vii. On-going training and sharing best practices to the study team members.

In essence on-site monitors will be promoted to a hybrid role that encompasses responsibilities of an on-site monitor, study manager and quality management– perhaps they will be called "Site Managers" in the years to come. This can become a positive change for sites, as monitors shift focus from QC activities to support activities that improve skills and mitigate against occurrence of quality issues that can be found in regulatory inspections or quality assurance audits.[3-7,13-15]

RBM enablement modified site monitoring processes

Conventional monitoring visit reports have the capability to record observations pertaining to conduct related to ICH-GCP and scientific compliance. However, these reports are verbose and not data oriented (largely containing information in complex prose rather than structured data that can be processed, organized and analyzed). In light of the aforementioned processes and activities that will be carried out by the on-site monitors, the methodology and format of recording objective data points related to site processes and assessment of the monitor need to complement if not replace the current SMV report.[3-7]

Software technologies can help capture inputs from SMV reports and derive overall site performance or risk assessment indication. Taking this approach will ensure that the site's performance and "story" is looked at from all angles; not just determined by recommendation from remote data scientists and analysts. Also, the transparency of such a report when shared with in-house or remote review can direct focus on areas of improvement & remediation.

As discussed in "RBM enablement modified monitoring visit preparation" on-site monitor will review central review report shared by central monitor and will prioritize his monitoring activity. By this approach monitor will be more focused for the actionable and will be optimize his onsite monitoring visit.[3-7]

POST MONITORING VISIT AND ON-GOING SITE MANAGEMENT (FOLLOW-UP PHASE)

Once on-site monitoring visit is completed and an objective report completed, it is important that open issues as well as certain risk indicators are visible for both on-site monitors and remote/central monitors. This will enable the alignment of both groups to the quality and risk mitigation progress being made at the site.

One of the key shortcomings in conventional clinical operations practice is unstructured communication of new risks or potential quality & safety issues that on-site monitors need to address. These aspects are often communicated by emails that get forgotten, lost and not tracked when a new on-site monitor transition occurs. Site level problems are considered in isolation and not assessed as a possible cross-site risk. Updates in clinical monitoring and management plans take long cycles that result in delayed updates to the monitoring plan and sometimes a consequent redundancy of the monitoring

plan. Such practices frequently result in monitoring deficiencies and protocol deviations that could have been avoided.[3-7]

RBM enablement post visit activities and ongoing site management

Applications for reporting KRIs and KPIs can present common information (e.g. dashboards) to site and remote monitors alike to ensure alignment. Also, it has to be acknowledged that even the best of risk plans will not be flawless, and we recognize that the risk profile of a study or program can change during its conduct. As we go through the learning curve in adopting RBM, it is also more likely that significant unexpected risks that could affect study outcomes will be discovered; these must be immediately provided to the clinical study management team so that proper review and relevant updates of RACT & IQRMP are made on a continual basis and risk mitigation steps applied by monitors across all sites in the study. The study team must commit to reassess and update these study guides on a continual basis for the benefit of patients, sites and the study team. Hence, the RACT & IQRMP need to be "living documents" with the most recent effective version available to all in real time. Technology solutions can make the IQRMP centrally available and version controlled with easy pathways to update its various components, enabling the vision of the IQRMP as the living roadmap to study oversight that all participants can easily access and follow across the life of the study.[3-7]

CONCLUSION

Significant progress is being made in the central/ remote monitoring space to realign roles and processes to a risk based monitoring model. However, risk planning as a collaborative process across functional groups is still in its infancy and effective solutions are needed to ensure the risk management plan can be updated quickly as needed and is placed at the heart of decision making by all groups. In addition the insights that drive governance are still often derived from technology solutions using a single source of data (such as the EDC or CTMS) that provide only one dimension of site performance and data quality and do not provide easy alignment of site and remote monitoring teams through transparency of information gained in the SMV process. It is time for us to look at on-site monitoring and management processes and make the necessary modifications. Such an intervention when coupled with technology alignment can significantly benefit the net outcome of monitoring as a discipline and the quality of life of sites and their monitors. Transformation from traditional monitoring method to RBM solution will significantly improve quality and will also reduce manual efforts of the On-site monitor. The challenges may arise as a result of implementation RBM solution, which may tackle by adopting change management technique and repurposing of study staff.

Disclaimer

The paper is an reflection of author's views only, and does not reflect companies view on the same.

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