

Review Article

Barriers, adoption, technology, impact and benefits of risk based monitoring

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ABSTRACT

The expense and unpredictability of clinical trials have increased drastically as of late. Up to third of a clinical trials expense can now be credited to the customary on location audit of trial information. While powerful observing is basic to ensuring the prosperity of trial members and keeping up the respectability of definite results, it is presently by and large acknowledged that the procedure for clinical trial checking needs to change. A more brought together, hazard based methodology is currently the favoured technique for monitoring clinical trials, as per a few administrative offices, including the US Food and Drug Administration (FDA). The movement has demonstrated overwhelming to numerous associations, nonetheless, and it is now and again not clear where to start. Over the previous decade, the clinical research industry's standard to meet regulators monitoring commitments has included continuous and normal onsite monitoring visits with 100% source information confirmation (SDV). The conviction that "more is better" proceeds with new proof that onsite monitoring practices don't inexorably ensure persistent wellbeing and data quality.

Keywords: Risk based monitoring, Source document verification, Targeted monitoring, Triggered monitoring, USFDA, MHRA, EMEA, Triggers

INTRODUCTION

Current Scenario in clinical trial demands that pharmaceutical companies find ways to reduce clinical trial complexity, drug development costs, and get more value from limited research and development budgets. Various regulatory agencies such as the U.S. FDA, MHRA and EMEA have determined that due to the high resource demand and cost of the traditional approach to clinical trial monitoring there is a need to find more efficient ways to accomplish this much needed, but costly endeavor. Risk Based Monitoring can enable life sciences companies to target and prioritize resources around identifiable risks relating to the safety of subjects and quality and integrity of clinical trial data.

UNDERSTANDING RISK BASED MONITORING

Risk Based Monitoring (RBM) can be depicted in a few unique ways. It can incorporate Reduced Source Document Verification (SDV), Targeted Monitoring and/or Triggered Monitoring. Source Document Verification has generally been done on 100% of information focuses gathered in a clinical trial. Reduced SDV limits the measure of SDV at the study, site and/or subject level. Targeted Monitoring is a method for decreasing SDV to a focused on number of data points. Triggered Monitoring sets a trigger which can be characterized as the identification of an issue or measure of information exceptional that requires SDV. Ideal RBM procedures fuse Targeted, Reduced and Triggered Monitoring.^{1,2}

In the FDA's draft Guidance for Industry Oversight of Clinical Investigations - A risk-based approach to monitoring, they speak of risk-based monitoring as an alternative approach to "frequent on-site monitoring and 100% data verification for all trials".¹ One of these option methodologies incorporates utilizing remote, monitor like assets, in a centralized or in-house monitoring role. Different methodologies include utilizing innovation both as a specialized device with investigative destinations or sites and as a device to oversee risks all through the clinical trial. The best RBM methodologies include finishing a study risk evaluation to build up a checking arrangement that best suits the study.^{1,13-15}

COMPARISON WITH TRADITIONAL WAY OF MONITORING VERSUS RISK BASED MONITORING

Data quality, patient safety and optimal resource allocation are the essential objectives of risk based monitoring. In the last two years since publication of the important EMA reflection paper and guidance - methodologies, products and services for risk-based monitoring have proliferated and diversified. The biopharmaceutical business can look over an assortment of general methodologies and particular practices to accomplish the fancied objectives. The way to deal with SDV is fundamental to any monitoring methodology, risk based or generally. In any case, as befits a procedure that is to a great extent unaltered from the time of paper-based clinical trials, SDV is mostly about detection and correction of errors after the fact. Centering the examination of risk based monitoring in light of SDV has a tendency to downplay other imperative parts of risk-based monitoring, for example, proactive quality administration and error counteractive action.^{10,21}

USE ENHANCED COLLABORATION, DATA REVIEW AND TECHNOLOGY UTILIZATION TO MITIGATE RISK WITH CENTRALIZED MONITORING PRINCIPLES

With medication improvement expenses taking off even as endorsement rates decrease, the quest for worth driven procedure changes has come to rushed levels. Numerous sponsors are turning their thoughtfulness regarding risk-based monitoring as an admission to moving flow within the industry.

The interest for more key ways to deal with clinical trials has distinguished risk-based monitoring, which tries to dispense resources mindfully without trading off clinical quality. The variables of data integrity, protocol compliance and patient safety - among others - affect how the assets are utilized, in conjunction with a far reaching risk assessment. The subsequent monitoring arrangement requires the continuous estimation of key risk Indicator's (KRIs) and patterns that, thus, trigger escalations and de-escalations of monitoring efforts.^{23,24}

IMPACTS OF CENTRALIZED MONITORING

Risk evaluation and administration are overwhelming the industry now as regulators look to help with inspiring medications to advertise in a leaner and more streamlined style. One of the fundamental needs of risk-based monitoring is to impact a decrease in reiteration, which should result in the removal of silos, the fostering of collaboration and the enhancement of coordination between sites and data managers.

Multidisciplinary groups including individuals with an aptitude in clinical monitoring, data analysis and safety surveillance should be best positioned to reap the full rewards of risk-based monitoring. These cross-useful groups ought to be adjusted to pinpoint scientific, medical, regulatory and operational risks, and then have the ability set to cure any inconvenience spots.

The simultaneous movement in tasks, roles and responsibilities can be uncomfortable for those involved, as those dug in well-known undertakings can approach another procedure with fear. On the other hand, all things considered group's network, individuals ought to feel enabled to exclusively react to KRIs that fall under their specific areas of expertise.

With restricted time and assets compelling every last clinical trial, a risk-based methodology considers the emphasis to dwell on the important aspects and the most critical data. The dynamic way of this methodology grasps nonstop change over the strategy of characterizing a risk assessment from the very beginning and staying with it all through the study.

By pinpointing the most core data and defining risk ahead of schedule in the process as could be expected under the circumstances, the Sponsors and CRO make the most all-encompassing environment for a solid operational procedure. Outfitted with a risk mitigation strategy, both sides can push ahead in quest for data transparency as part of the monitoring plan.³⁻⁵

CAN RISK-BASED MONITORING SAVE TIME AND MONEY?

In the terrifically essential zones of time and money, it is maybe the capacity to assess all the information gathered at one time where the best profits will show up.

Less information focuses and site visits ought to free up more consideration for the real patients, and more precise data analysis should result in a better ability to spot trends earlier in the process. Risk-based monitoring ought to make a clearer vision for the master plan of the study, lending crucial context to the process.

Upgraded capacity to total extensive datasets while decreasing the measure of data that researchers are required to survey ought to streamline the study also. In

time, the utilization of statistical techniques ought to find up to such checking procedures, taking into consideration the utilization of reported information to direct the audit and confirmation forms. The trust is that the mix of information streams will prepare associations to improve educated - and prior - decisions.^{7,8}

USE OF TECHNOLOGY IN RISK BASED MONITORING

Currently in market there is several remote data capture (RDC) and clinical trial management systems (CTMS) available which can support a risk based monitoring approach. Few systems are also available wherein Clinical trial data are entered and reported manually. Hence there is need to develop or setup more advanced systems for flagging or alerting automatically data to review and these alerts can be developed for notify those who need to take action when an issue exists.

The CTMS system ought to guarantee that all data captured onto monitoring visit reports (MVRs) information to be gathered into a database for reporting and examination which will help in hailing different issues. It is most troublesome assignment to oversee clinical trial risk encompassing danger based checking. A few of the measurements identified with danger are assessed by screens amid their observing visits and gathered onto their MVRs. Having the capacity to break down the information entered onto the MVR can signal when an issue exists at a specific site.²³

Electronic data capture (EDC) system could encourage the move far from dependence on location observing by effortlessly taking into consideration the execution of centralized monitoring methods. A few critics of risk-based monitoring point out that the study group must know how to make ideal utilization of chosen technologies. All things considered, numerous industry regulators still ask why profitability has not all the more nearly took after innovative advances inside of the business throughout the years.

Around there, EDC has the adaptability and capacity to execute proficient risk-based monitoring; however there are some bureaucratic obstacles to overcome in connection to interpretation and different issues. All things considered, the technology serves as a piece of the checking arrangement, just not the aggregate arrangement.²²

STILL BARRIERS TO OVERCOME IN THE ADOPTION OF A NEW MONITORING APPROACH

Risk-based monitoring can enhance the nature of data oversight with the goal that organizations can distinguish potential risk prior and make remedy move if fundamental. There is no denying that there are characteristic difficulties included in tending to

observations about what is marked "offsite monitoring" in a few quarters. Also, measures must be taken to guarantee that sites are not learning about overlooked or cut of the circle, with an end goal to expand on and keep up strong associations with sites.

The industry in general has long been seen as traditionalist in its eagerness to adjust to new advances and developments, so it will tumble to all included to not just make a solace level with risk-based monitoring, however paint a photo that will offer the business everywhere some assistance with seeing how ideas can decipher into clinical achievement. Just along these lines, will supporters of unified observing have the capacity to conquer the customary receptive nature of the business by influencing adversaries toward a more proactive, forward-looking methodology.

Furthermore, rate of profitability may not be rapidly obvious with regards to risk-based monitoring. Because of this absence of confirmation in regards to prompt advantage, biopharma organizations and CROs should be arranged to answer questions about error detection and the ability to adjust KRIs mid-trial, among other queries. It is likewise essential to perceive that, for patient protection, protocol adherence and other issues, in-person site visits are crucial. Truth is told, by lessening the time required for SDV checks, clinical research associates could be authorized to invest more onsite time on targeted responsibilities. Also, by nearly monitoring KRIs and incorporating targeted, triggered strategies into the bigger arrangement, the group will be all around arranged to distinguish when onsite audits are essential based on these indications.

The fact of the matter is that, contingent upon the study, a risk-based monitoring methodology could uncover that site visits once at every three months intervals are adequate, or that site visits each six to eight weeks may not be sufficient. At the point when risk-based monitoring can be seen as an approach to completely underwrite - with an exceptional level of quickness - on prescient capacities, then the tide will have turned.

BENEFITS OF A RISK-BASED MONITORING

When a risk-based monitoring system incorporates a centralized, real-time overview of the data with well entrenched risk detection and mitigation strategies, the result is one of the industry's most effective tools for managing a clinical trial, proactively. Such a system:

- Identifies problems early so that they can be remedied quickly, protecting patients and preserving the overall integrity of the study.
- Improves the efficiency of CRAs, as they concentrate on the sites that need help and allow competent sites to proceed without unnecessary interference.

- Dramatically improves the reliability and verifiability of study data, avoiding unpleasant surprises upon regulators' review.
- Has the potential to reduce overall monitoring costs in most studies.

Despite the relative immaturity of risk-based monitoring, preliminary data suggests that this solution is providing equal or superior results to the classic 100% SDV process. Many companies are shifting to this more efficient model with several large studies well underway using the methodology.

Given that the FDA “encourages greater reliance on centralized monitoring practices than has been the case historically, with correspondingly less emphasis on on-site monitoring,” the path is clear for companies to take full advantage of what technology can offer. With the proper system, risk-based monitoring is an effective way to meet the growing challenge of ensuring that the study protocol is being correctly interpreted and executed, resulting in proper patient care and valid study results whilst simultaneously reducing clinical trial costs.

ADOPTION OF RISK BASED MONITORING

According to the MCC survey, which allowed respondents to make more than one selection, the top three primary reasons for adopting RBM were:

- Reducing monitoring costs (78% of respondents)
- Improving data quality (66%)
- Improving quality oversight (66%)

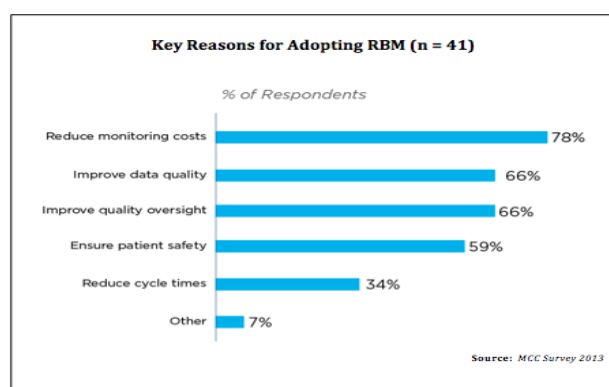


Figure 1: Reasons for adopting RBM.

These percentages are the group mean; when broken down by type of respondent type, the results vary. For CROs and academic research institutes, for example, the key driver for adopting RBM was reducing monitoring costs (92% and 83%, respectively); whereas for pharmaceutical companies, improving quality oversight was the top reason (83%). For biotech firms, improving data quality was the major reason (83%).⁸

The FDA guidance identifies human subject protection and data quality as the overarching goals for RBM, and

although these concerns differ somewhat from the survey findings, generally, they are closely aligned. Survey results are also similar to the purpose for RBM as stated in the 2013 Reflection Paper from the EMA. The Reflection Paper focuses on the need to overhaul the costly system of oversight to improve quality assurance and quality control in clinical trials and suggests that electronic solutions should be considered (see sidebar). As mentioned earlier, these two factors were among the top three reasons cited in the survey for adoption of RBM.⁸

WHAT LIES AHEAD FOR RISK-BASED MONITORING

The FDA first offered guidance on a “risk-based approach to monitoring” in 2011, with a document offering direction on industry oversight of clinical investigations. Subsequent guidance sought to deliver the kinds of details and specifics that could support small and mid-size sponsors that were struggling to develop their own risk-based plans, culminating most recently in August 2013’s finalized guidance.¹

Risk-based monitoring is most often employed in Phase IV studies, but the hope is that the most recent FDA guidance will open up usage in Phase II, III and IV trials by addressing concerns about quality and efficacy. Perhaps the most important takeaway from recent guidance is the FDA’s insistence that there is no single monitoring approach that is right for every trial, with a recommendation that plans are designed to the trial’s highly specific data integrity and safety needs. In effect, the FDA is encouraging centralized monitoring where appropriate, with recognition that there are other ways to ensure quality monitoring without mandating on-site monitoring and 100-percent SDV.^{16,17}

At its best, risk-based monitoring could play a role in reducing costs, more efficiently deploying limited resources and jumpstarting stagnant pipelines. And with efforts such as the Clinical Trials Transformation Initiative underway, it may be difficult to put the genie back in the bottle when it comes to risk-based monitoring. The topic has become a red-hot issue within the industry, and such interest creates the kind of momentum that could overcome the conservative nature of the industry.

When done correctly, risk-based monitoring can allow for the proactive mitigation of likely sources of error, rather than the reactive correction of errors that have already happened. When the focus is on pinpointing high-risk areas, critical data and likely sources of error, the quality of the data that could compromise patients or data integrity is ensured.

Efficient resource allocation and the prospect of free-flowing pipelines sound great in theory, especially when the interests of patient safety and data quality can be

simultaneously furthered. In the end, however, adoption will be slow until concrete examples of cost reductions can be shared - a development that some see just over the horizon.

CONCLUSION

To run fruitful clinical trials in today's surroundings of expanded clinical trial observing assets and expenses, the clinical trial industry must hope to fuse better approaches for deduction into checking procedures. Administrative Agencies have as of now held onto new thoughts, for example, danger based observing while as yet guaranteeing that patient wellbeing is all around oversaw and information quality what's more, honesty is not traded off. Drawing closer hazard based observing strategically can bolster your business by diminishing the expenses of conventional on location checking while utilizing new advancements to oversee hazard. The outcome is a quicker time to market, decreased observing expenses and concentrate on quality included undertakings. At the point when done right, hazard based observing turns into the most ideal approach to supervise clinical trials.

It would be impractical for a regulatory agency to mandate a one-size-fits-all approach for the implementation of a risk-based monitoring solution. Although a challenging frontier, the open-ended framework of the draft guidance allows sponsors to customize a solution that works best for their individual profile. With their rich history of paper-based documentation and manual processes, companies entered the millennium with their own unique infrastructures and technology profiles. Conforming to a single risk-based monitoring methodology would be nearly impossible if it meant abandoning current practices and divorcing infrastructure assets.

Pharmaceutical organizations that conduct clinical research in the most productive and consistent way will amplify the arrival on their decades-long foundation and innovation speculations and position themselves to make substantial determinations about propelling a specific medication or treatment program through the improvement pipeline.

Despite helpful region or size of clinical trial, sponsor must grasp and receive the precepts of risk based monitoring in the connection of the predominant worldwide IT construction modelling. This will empower them to meet the regulatory necessities relating to the assurance of exploration subjects and convey engaged and exact supporting information to controllers. Supports that do this will likewise impel their current innovation resources into a system for responsive, agreeable, exact and shrewd clinical trial plan and direct.

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