Research Article

A Pilot Study to Understand the Challenges and Benefits of Implementing Risk Based Monitoring in Clinical Research

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Abstract

AIM: *To understand the challenges and benefits of implementing Risk-based monitoring in clinical research*

METHODOLOGY: *A survey-based study was conducted by taking feedback from 30 clinical research professionals with the help of a validated questionnaire comprising 10 questions. As it was a pilot study the analysis was a very basic one by using a percentage method.*

RESULTS: *73% consideration is for risk-based monitoring (RBM) to be a quality-driven initiative with 90% accepting the fact that, implementing RBM will help to reduce the frequency and extent of on-site monitoring and increase the effectiveness of on-site visits. As the model is new, lack of training and knowledge takes up the lead with 90% as one of the barriers to the RBM model.*

CONCLUSION: *Additions of tools to the RBM model will help in better acceptance by the industry, the model has its benefits with some barriers but the on-site monitoring will continue to play its role in the field of clinical research.*

Keywords: *Risk-Based Monitoring, Clinical Trials, RBM, Benefits of RBM, Barriers in Implementation of RBM, key aspects of RBM, Monitoring.*

Abbreviations

AE: Adverse Event

CRF: Case Report Forms

CRO: Contract Research Organization

ICH-GCP: International conference on Harmonization: Good Clinical Practice

RBM: Risk-based Monitoring

SAE: Serious Adverse Event

SDR: Source Data Review

SDV: Source Data Verification

SLA: Service Level Agreement

SOP: Standard Operating Procedures

US FDA: United States: Food Drug Administration

Background

Introduction

Clinical Research as an important branch of the healthcare industry plays a role by testing the safety and efficacy of the drug, device, biologicals, etc. in the human body giving the complete knowledge on its pharmacological parameters and confirming the safety with a confirmation of the optimum dose.

To confirm the safety, right, and well-being of these trial subject and to ensure the conduct of the trial is in adherence to GCP, Protocol, Regulatory guidelines, and SOPs; it becomes utmost important of one to conduct a good quality monitoring which ideally used to be done by going to the respective site and checking all the necessary documents and processes in person. **(**9**)** The benefits of traditional monitoring included identifying data entry errors (e.g., discrepancies between source records and case report forms (CRFs)) and missing data in source records or CRFs, assuring that study documentation exists, assess the familiarity of the site's study staff with the protocol and required procedures, assess compliance with the protocol, investigational product accountability, etc. **(**9**)**.

The Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring (DRAFT 1) released in August 2011 was a replacement for the Monitoring guidance document of 1988 to adapt to the changing environment of clinical research. Which explained the strategies for monitoring activities that reflect a modern, more risk-based approach that focuses on critical study parameters and relies on a combination of monitoring activities to

oversee a study effectively." In addition to removing the stigma that 100% source data verification is the only way to product approval, FDA is encouraging sponsors to take credit for activities that are conducted throughout the study that contribute to the responsibility of monitoring investigations. Many of these activities take place in-house outside of the traditional field monitoring role and are referred to as "centralized monitoring." **(**1**)**.

ICH than rolled-out the Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) which includes electronic records, data capture systems, risk management, and monitoring plan and is now considered as a standard set of guidelines which is accepted by the industry. **(**5**)**.

RBM is said to be moving away from 100% SDV of patient data. It employs various tools, platforms, and dashboards to identify signals, which indicate potential issues with trial conduct, safety, data integrity, compliance, and enrolment. This allows the study team to concentrate on high-value tasks and focuses resources on specific trial-related matters. (quanticate.com) One major area that has proven confusing to sponsors, is how centralized or remote monitoring should relate relative to more traditional on-site monitoring. SDR and SDV, for instance, traditionally have been conducted via on-site visits, and it is unclear whether a sampling approach, which could be conducted under a more centralized monitoring scheme, would be acceptable for these activities. **(**6**)**.

Another key factor is change management, RBM is not a "set it and forget it" process, because the risk is complex and can change as a study progresses, companies must not consider RBM as a single risk assessment, but a continuous improvement concept. **(**6**)**.

Implementation of RBM

At the planning stage itself, every clinical trial should be assessed for alternative monitoring strategies based on several factors, including what is being studied, protocol complexity, and experience with similar trials. The risk assessment will serve as the foundation for all successive steps in the RBM strategy. An assessment would include the following:

- Defining the data and processes critical to patient safety and data quality.
- Identifying the risks and creating processes to minimize them.
- Setting indicators and thresholds that will trigger an investigation and/or corrective action.

Implementing RBM can be challenging, but it is not impossible if certain steps are taken.

To achieve success, sponsors, CROs, and sites should consider:

- Identifying areas of greatest risk based on previous experience with similar trials and developing metrics to quantify potential risks.
- Assigning roles for staff, along with providing written operational instructions.
- Creating decision trees for responses based on failure events.
- Mapping the relationships between clinical and operational data.
- Composing a monitoring plan to coordinate activities between the members of the project team.
- Implementing training on RBM strategies for all team members (Lynn).

Key Aspects of the RBM Plan

Defining Key Risk Indicators: An RBM plan should define the key risk indicators, their metrics, and the thresholds for corrective actions based on the performed risk identification and assessment. **(**2**)**.

Describing Monitoring Approaches: A risk-based monitoring plan is different than the traditional monitoring plan, as it uses various monitoring approaches like centralized monitoring, on-site monitoring, and off-site monitoring and also shares the responsibilities with various cross-functional resources. It should clearly describe the monitoring approaches to be used regarding what should be achieved through centralized monitoring and what should be done during on-site visits and off-site monitoring for controlling and mitigating various types of risk/issue(s). An RBM plan is considered a "dynamic" plan, as the frequency and extent of on-site and off-site monitoring activities will vary based on the critical risk/ issue(s) findings, the performance of the sites, the quality of data coming in from different sites, and the identification of new risks. For instance, the sites that are not performing well or are having more quality issues will receive more attention or on-site visits than the sites which are performing as, or better than, expected. An RBM plan must also suggest the process to manage unresolved key issues or significant instances of sites' non-compliance. **(**2**)**.

Roles & Responsibilities of Various Functional Areas: Development and implementation of an RBM plan require expertise from cross-functional areas like clinical operations, the medical

team, the data management team, biostatisticians, and the technology group. The roles and responsibilities of a central monitoring team, on-site monitors, data management, and technology groups should be clearly defined for the successful implementation of risk-based monitoring. **(**3**)**.

Communication Plan & Documentation: The RBM plan must describe the system/tools used for documenting centralized monitoring activities. It should clearly outline the communication plan for various stakeholders and the documentation process for centralized monitoring reports, issue escalation, coordination between the centralized monitoring team with on-site monitors or relevant stakeholders for risk control or issues resolution. An appropriate communication plan is crucial for global studies. Similarly, efficient coordination among data management, technology, and centralized monitoring teams is important to ensure the timely identification of risks. The RBM plan must also mention the events where a plan needs to be revised based on the identification of new risks and amendments to protocol, etc. **(**2**)**.

Technology Used: The RBM plan should include information about the technology/tools used and the various sources that provided the relevant data to create planned analytics reports to monitor risk/issue(s) related to data quality, patient safety, and trial operations. **(**2**)**.

Overall Quality Management: The plan should explain training requirements for the altered process, especially with the introduction of a centralized monitoring process. The monitoring of quality, efficiencies metrics, and planning audits help build overall quality and in evaluating the RBM implementation process. **(**2**)**.

Centralized Monitoring can be effectively used for "Oversight" of:

- Critical risk areas and critical success factors.
- Clinical investigations and investigational sites' performances.
- Subject safety aspects (study drug-related safety issues, number of drop-outs due to AEs/SAEs, etc.).
- Internal and external (CRO/Vendor) team performances and efficiencies, SLA (Service Level Agreement) management.
- Protocol and regulatory compliance.
- Implementation of key strategies and their outcomes.

- Overall quality, timeline achievements, and budgetary spending **(**3**).**

Benefits of Risk-Based Monitoring (RBM):

Lower costs: More than a quarter of the cost of a clinical trial is tied up in monitoring activities. Therefore, if we can optimize the monitoring, we can significantly lower the costs.

Faster and focused results: Due to data analysis and centralized monitoring, the results are faster and more accurate.

Low error rate: When compared with traditional studies, RBM studies have reduced the number of missing pages by 45% and brought down the critical data error rate by as much as four times.

Real-time data entry: RBM encourages real-time data entry. Comparative studies show that sites that deploy RBM are 5 times more likely to enter study data within 7 days.

Better focus on the primary objective: Personnel has more time to focus on their core roles and responsibilities, as their administrative tasks reduce significantly.

Increased safety: With admin tasks reduced, resources can be allocated more efficiently, and focused on ensuring the safety of participants.

Better compliance: Data-driven insights and other digital tools facilitate early detection of problems, improved site training, and identification of potentially fraudulent activities. These factors automatically result in better compliance.

Increased collaboration: RBM encourages more collaboration and sharing among co-workers. **(**10**)**.

Study Rational

Clinical trials are directly associated with the quality, may it be data or processor systems and the second pillar in clinical research would be right, safety and well-being of trial subjects, there all can be very well managed with the help of Monitoring activity which plays a very crucial role in the field of clinical research.

As and when the time progresses, we move ahead with the advancements and so in the process of Monitoring came the concept of RBM for which the initial guidelines were issued by US-FDA in August 2013. The concept of RBM was introduced to overcome the hurdles faced with traditional monitoring, such as it being time-consuming, expensive, mitigating risk in advance, etc. But the question still continued in the mind of many research experts like, will this continue to serve 100% SDV, what in case of highly complex protocols, how would SAE reporting be managed, etc.

The mentioned guidance focused on how sponsors should prevent risk to data quality, human subject protection and trial integrity. This guidance also prompted the industry to brainstorm on implementation of RBM and with the inclusion of RBM in ICH GCP E(6) R2, it is gaining importance, However, there are still some concerns in operationalizing this concept.

The common concerns that the industry is facing revolves around the authenticity of remote monitoring and barriers in implementation. Considering that RBM is the future of clinical research and is perceived as a critical means of improving patient safety, quality data and an overall reduction in trial cost the major aim of the survey was to understand how the industry personnel's looks at RBM and in their opinion what are the pros and cons towards its implementation.

Objectives

Primary Objective: To understand the challenges and benefits of implementing Risk-based monitoring in clinical research.

Secondary Objective: To identify any knowledge deficits and developmental needs of the clinical research professional in implementing risk-based monitoring.

Methodology

A qualitative methodology to explore perceived benefits and challenges of implementing a risk-based monitoring approach (using a questionnaire which was validated before implementation) was used to determine the perception of various clinical research professionals in India. Survey responses were requested from clinical research professionals having more than 6 years of experience in the industry with the help of a designed questionnaire. Thirty professionals participated in the survey, out which seventeen had an experience of RBM and the other thirteen had an experience of complete traditional monitoring.

The study was a complete survey-based. It took nearly 2 months to get responses and to meet the desired responses from 30 individuals (40 forms were distributed).

The complete process is explained in the flowchart below (Figure-1):

Figure 1: Flow-chart explaining the complete methodology

Results and Discussion

This pilot study (survey) was conducted amongst research professionals where 30 individuals could participate of which 57% (17 participants) had an experience of working with the RBM model and 43% (13 participants) have only worked with the traditional model.

The study indicates that on-site monitoring will always have a role to play in SDV, implementation of RBM can be challenging. **(**4**) (**1**)** where the response received was 90% (27 participants) who agree to it (Figure -2).

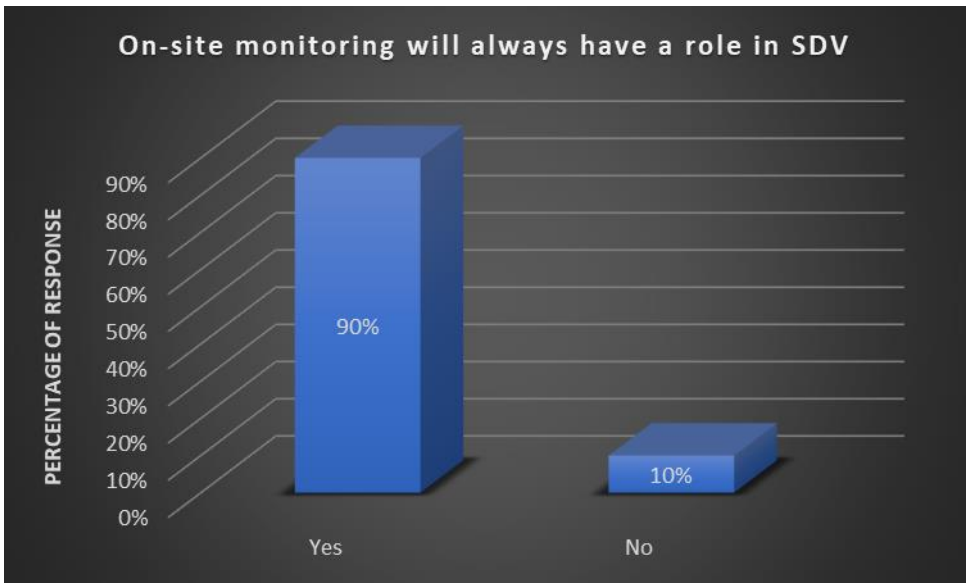

Fig 2: Response to "On-site monitoring will always have a role in SDV

RBM as an add-on to the traditional monitoring should be a quality-driven initiative that will utilize a flexible approach to monitoring and would help a monitor to enhance the quality of the trial and would also help in reducing the frequency and extent of on-site monitoring. 73% (22 participants) agree to the fact and results continue to be in line with the literature.

"The sponsor should develop a systematic, prioritized, risk-based approach to monitoring to monitoring clinical trials" (GCP2.0) **(**3**)** as stated under industry guidance; the results from the conducted survey(Figure -3) says that centralized monitoring can be used for oversight of critical risk areas and success factors with 73% (22 participants) followed by the protocol and regulatory compliance with 60% (18 participants), overall quality timeline, achievement and budgetary spending with 47% (14 participants), clinical investigations and investigational site performances and subject safety aspects sharing 43% (13 participants) each implementation of key strategies having 40% (12 participants) and the minimum acceptance for internal/external team performances 23% (7 participants).

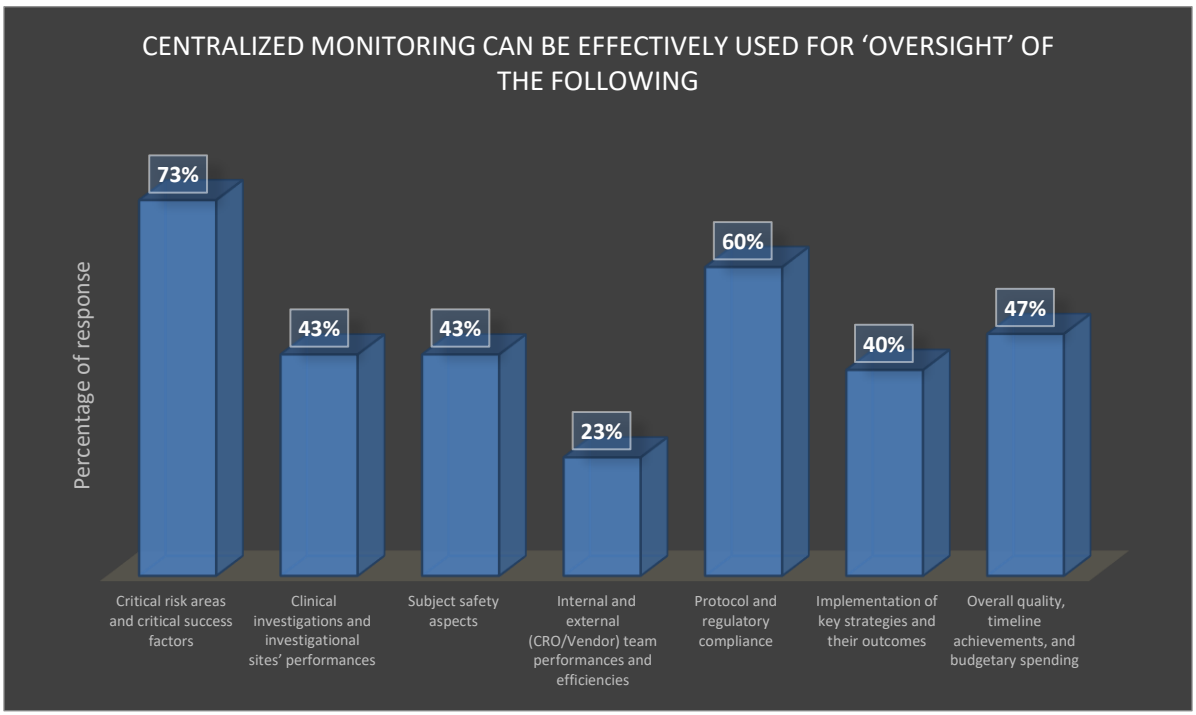

Fig 3: Benefits of Implementing RBM

Industry guidelines mentions, "additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data" **(**2**)** (GCP2.0) to confirm the same the survey results (Figure -4) indicate that key aspects of risk-based monitoring include providing the relevant data to create planned analytics reports to monitor risk/issue, training of personnel on tools to identify trends/issues, defining the key risk indicators, succeeded by describing monitoring approaches and communication plans for various stakeholders and cross-functional expertise with 93% (28 participants), 80% (24 participants), 67% (20 participants), 50% (15 participants) 43% (13 participants) and 33% (10 participants) respectively.

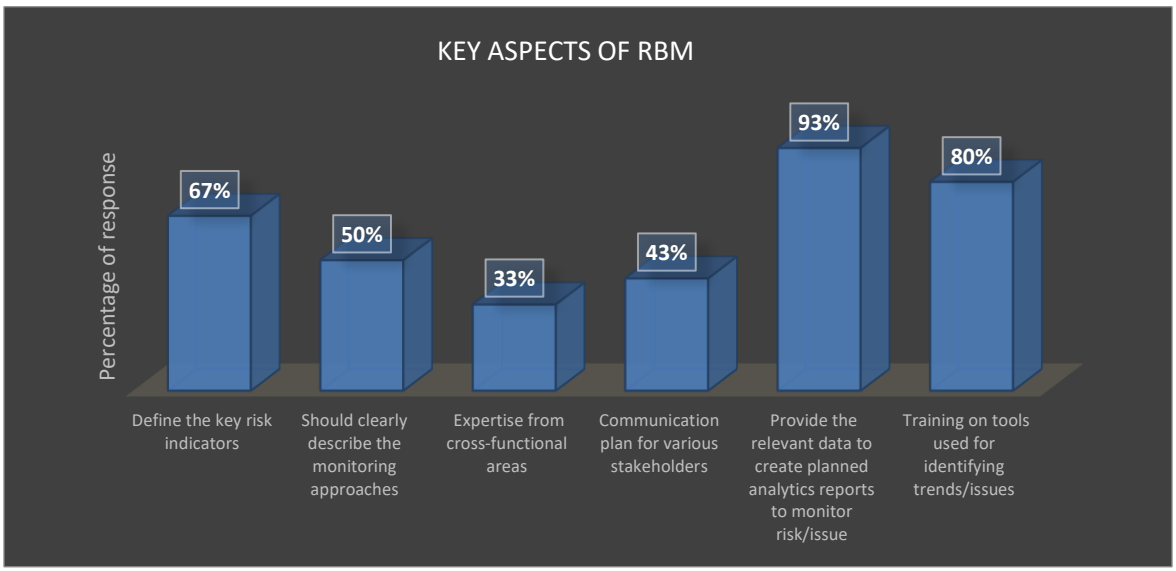

Fig 4: Key aspects of RBM

While talking about benefits and key aspects and to ensure the best implementation of the process it is always necessary to understand/identify the barriers associated in its implementation(Figure-5), based on the survey results these included lack of training/knowledge as the biggest barrier in the implementation of RBM i.e. 90% (27 Participants), followed by increased cost 73% (22 participants), next was insufficient verification 47% (14 participants), increased workload 23% (7 participants), others with 10% (3 participants) where traditional mindset and no working RBM plan during protocol development phase were mentioned. The available literature does confirm the same. **(**8**)**

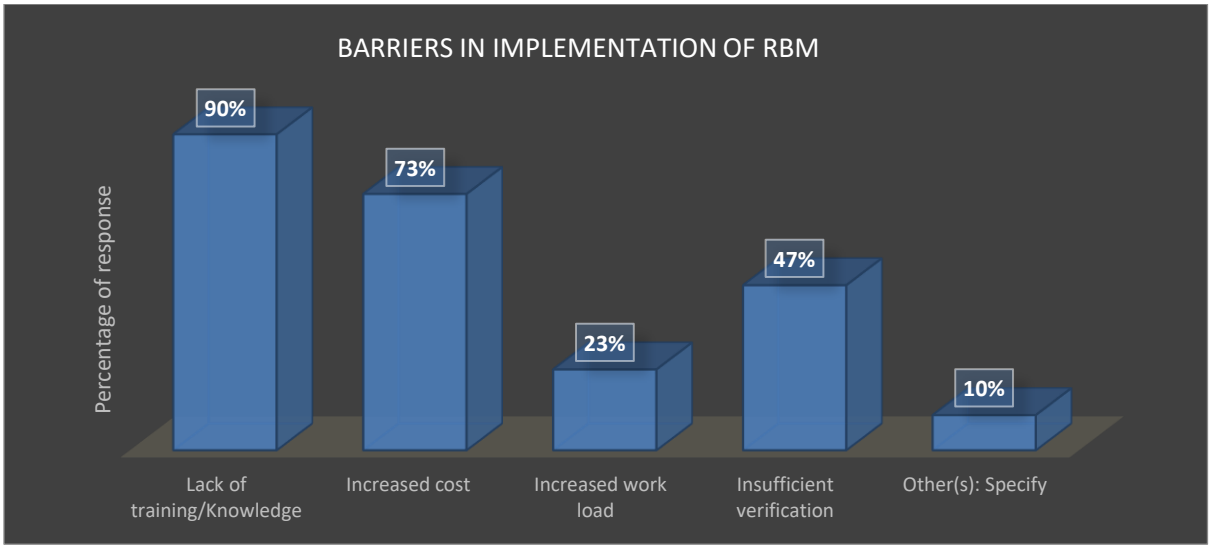

Fig 5: Barriers in the implementation of RBM

Reduce the frequency and extent of on-site monitoring and increase the effectiveness of on-site visits, proper risk-based approach, appropriate use of centralized monitoring and reliance on technology advances can help to meet statutory and regulatory requirements, using safety data, with the help of proper analytics, centralized monitoring helps in understanding AE/SAE trending, distribution, and outliers and optimize on-site visits by identifying risks/issues proactively and by keeping track of site performances, offers a smarter and more cost-effective way to enhance quality and monitor patient safety in an efficient manner and helps to understand site-specific issues or non-compliance are the benefits which were identified with the help of literature **(**10**)** and the participants of the survey do agree to the same with all the options getting selected by more than 50% of the participants except "understanding site-specific issue or non-compliance" which is also 47%, every value is detailed in the figure below(Figure-6).

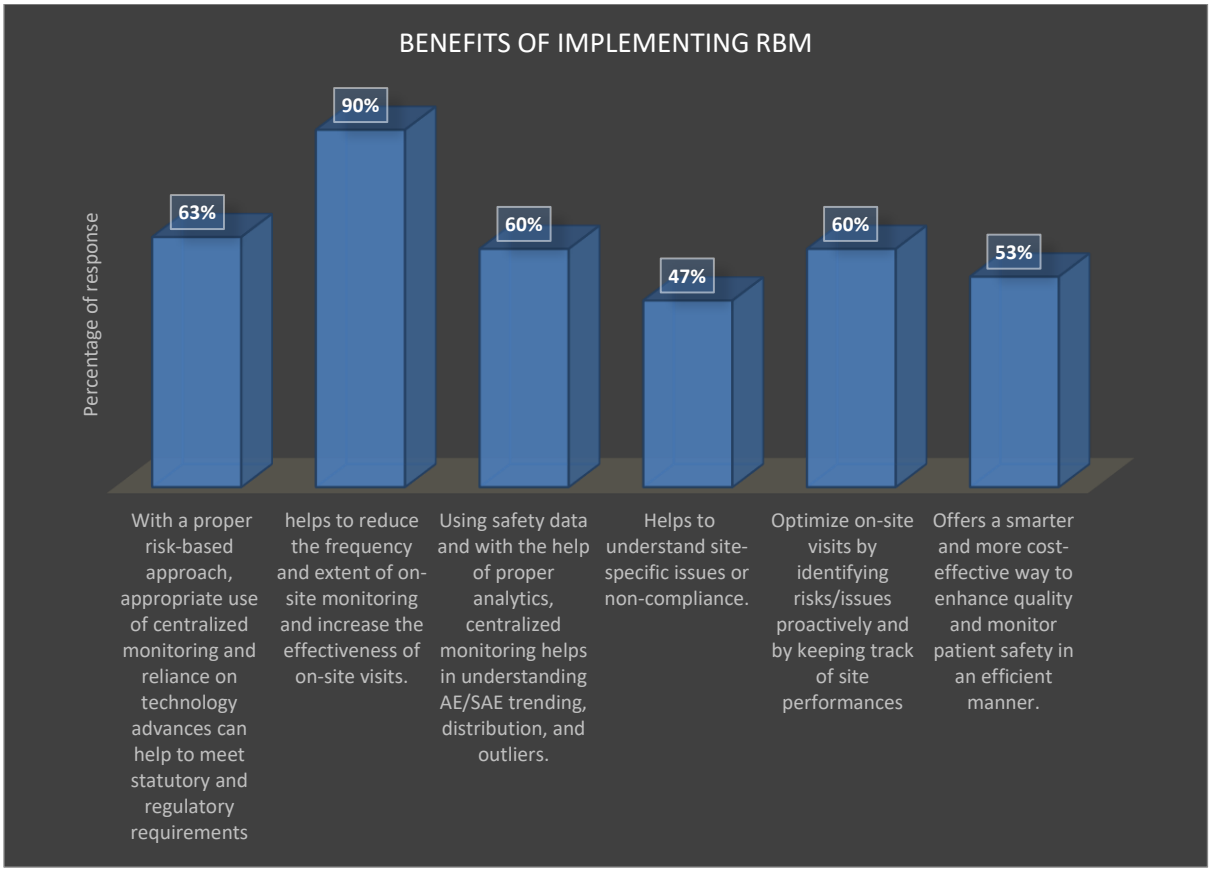

Fig 6: Benefits of implementing RBM

Conclusion

This study helps us in understanding the gaps, challenges, and benefits of implementing Risk-based monitoring in clinical research. Results showed that on-site monitoring will continue to have its importance SDV. A shift to the new RBM model will supplement monitors with effectiveness to meet regulatory requirements, timely reporting of AEs/SAEs, identifying risk and trends that follow. Developing new tools for various trial-related activities like identification of PDs, trend and missing data for RBM to become more effective will help the industry to accept the RBM model more effectively. Providing the planned analytics report to monitor will be the key aspects of RBM and implementation of RBM will help increase oversight on critical risk areas, protocol and regulatory compliance, overall quality timeline, achievement and budgetary spending, clinical investigations and investigational site performances, subject safety aspects, implementation of key strategies and internal/external team performances. However, the study indicates that implementation of RBM can be challenging and lack of training is one of the major hindrances in the implementation.

The generalizability of the results is limited as the sample size is very small (being a pilot study). Further research is definitely needed to establish the major barrier in the implementation of the RBM and measures of successful implementation in clinical research.

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