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Research Article

Understanding the Influence of RBM Model on Project Management

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Abstract

The industry is well suited to the traditional on-site monitoring practice and shift from this to central monitoring raises concerns for the professionals. Sponsors are shifting their focus from on-site monitoring to risk-based monitoring. Clinical research organizations are working hand in hand to support the sponsor organizations for successful implementation of new model. The risk-based monitoring model works on identification of risk areas. It is primarily crucial for the sponsors to identify and categorize the risk in terms of site level, study level and sponsor level for a study and develop ways to manage and mitigate these risks. The industry from the year of inception of concept of RBM till date is trying to carve a path for developing a guaranteed method of risk-based monitoring model implementation. Many Sponsor/CROs are struggling to find a pathway for successful implementation of RBM model. The survey tried to understand the influence the RBM model has had on the industry, especially on the project management aspect of it and we see that the survey data and the available published literature runs parallel.

Keywords*: RBM Model, management, sponsor, Steps for adopting RBM,*

Introduction:

The regulation requires the sponsors to conduct effective oversight to ensure protection of the rights, welfare and safety of human participants and the quality of clinical data submitted to the regulators. The regulations do not specify how the sponsors should conduct the monitoring and therefore considering the multiple factors, a board range of monitoring approached can be applied. [1]

Most monitors in the industry face high turnover. Issues like stagnant salaries, lack of upward mobility and extensive travel are amongst the biggest factors affecting the clinical monitoring turnover. ICH GCP section states that sponsors should select monitors who are qualified and experience, but it doesn't give description on what that means. Many monitors lack formal training and competencies before they independently start conducting monitoring activities. Hence, this leads to inconsistencies among monitors with different background and levels of training and experience. [2]

In the past two decades, the industry has seen a tremendous increase in number of global clinical trials and their complexity. These changes create new challenges with respect to clinical trial oversight, difference in clinical investigator experience, site infrastructure, treatment patterns, standard of healthcare and geographic variance. Additionally, increased use of electronic systems, improvements in statistical assessments create a pathway for alternative monitoring approaches which can improve the quality and efficient of sponsor oversight. [1]

At initiation of the study, each study must be assessed for use of alternative monitoring strategies. Several factors establish the alternative monitoring strategies, including what's being studied, the complexity of protocol and experience with similar trials. Assessment of Risk serves as the basis for the foundation of all successive steps in the RBM implementation. Risk Assessment involves:

- Defining the data and processes critical to patient safety and data quality
- Identifying the risks and creating processes to minimize risk
- Setting risk indicators and thresholds that will trigger an investigation and/or corrective action [3], [4]

As regulatory requirements continue to expand and vary between different countries and agencies, the severity of clinical trial monitoring is becoming complex. With sponsors employing traditional monitoring activities and increasing regulatory enforcement activity demonstrating that even with 100% data monitoring, the quality of data monitored still results in U.S. FDA's form 483 observations and missed opportunities for active risk mitigation.

The sponsors are seeing rise in FDA Form 483 observations and warning letters, the industry agrees that the time, cost, and associated risk with resolving non-compliance, data discrepancies and protocol deviations are no longer sustainable. The guidance document encourages a risk-based approach to study monitoring, sponsors are re-evaluating the traditional monitoring methods to improve quality, efficiency, and compliance.

Risk-based monitoring focuses on a systematic approach towards risk identification, enabling structured processes for the assessment, control, review, and adjustment of risk throughout the trial lifecycle. The RBM allows sponsor to focus on source documents, critical data points, site regulatory and protocol compliance ensuring subject safety and verification of data quality and integrity.

Currently, the sponsors are depending on only three traditional monitoring models which are traditional monitoring models- targeted onsite visits, statistical sampling model and/or triggered reactive model designed to answer the discrepancies or noncompliance issue.

As the cost of clinical sites are rising, and clinical teams must work with restricted budgets it is becoming difficult for sponsor companies to keep a tab on the cost whilst ensuring the quality results and regulatory compliance within the timelines. To add in with the growing number of activities that are outsourced to CROs, it is impossible to control the cost. The trial budget is affected with several factors and unexpected issues, forecasting a 100% real budget is difficult. However, companies can try to forecast the budget as close to the real budget. [5]

Well planned and structured clinical studies from timelines to database lock will lead to savings in the long run. Thus, the time to launch the product is shortened and ensures longer patent exclusivity. [6]

The shift in CRA focus and responsibilities is well known. Owing to this change the companies have created specialized monitor roles which are different from the 'traditional' CRA role. However, for mid-sized companies CRAs need to adapt and grow with the change. Hence change management must be the front-line objective of the effective implementation of the RBM model.

This change is facilitated with several support programs for the CRAs. CRA training is the key for an effective RBM model. This training must focus on comprehensive understanding of the trial, systems, communication skills, risk management plans. Specifically, targeted training on risk management strategies and decision making are important and this is not typically included in training plans for traditional CRAs. CRAs have the best knowledge of the site and this knowledge should be used in assessing and adapting monitoring plans, which are essential for successful implementation of RBM.

Clinical trial managers should provide independence to the CRA level with RBM, as CRAs should be part of the feedback loop for risk identification, risk assessment and decision making. CRAs must be involved in the risk assessment of the site throughout the study instead of assigning CRAs with targeted visit schedules based on risk data. [7]

Methodology:

The survey is conducted among clinical research professionals having more than five years of work experience in the field of clinical research. The forecasted data collection timeline was of 15 months. The statistical tool was used to calculate the sample size for this project by the biostatistician involved in the study. The statistician confirmed that the projected sample size for this study should be 500 however, a sample size of 300 is considered as fair and 1000 as excellent. The survey was available on the electronic portal and the link to the survey was shared with participants using various modes of communication like mail, phone, social media etc. This study used a quantitative method to collect data. The basic techniques for analyzing quantitative data were examined.

Results:

The questionnaire was sent to multiple clinical research professionals worldwide. However, the complete response to the questionnaire was received from 511 participants.

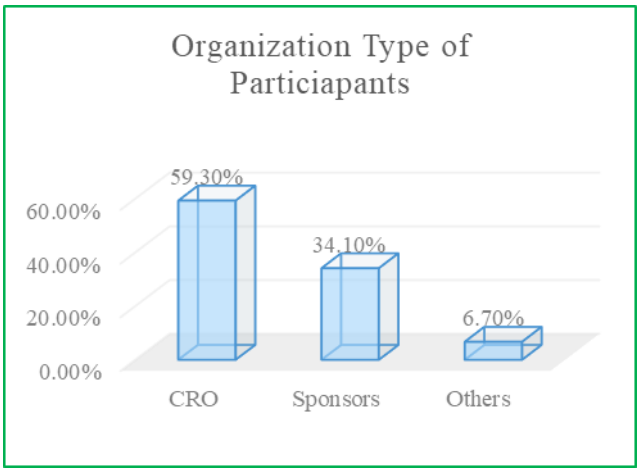

Figure 1

59.3% (303 participants) of the respondent's current organization is CRO, while 34.1% (174 participants) work for sponsor companies, and 6.1% (34 participants) work for other type of organization i.e., Site Management Organizations.

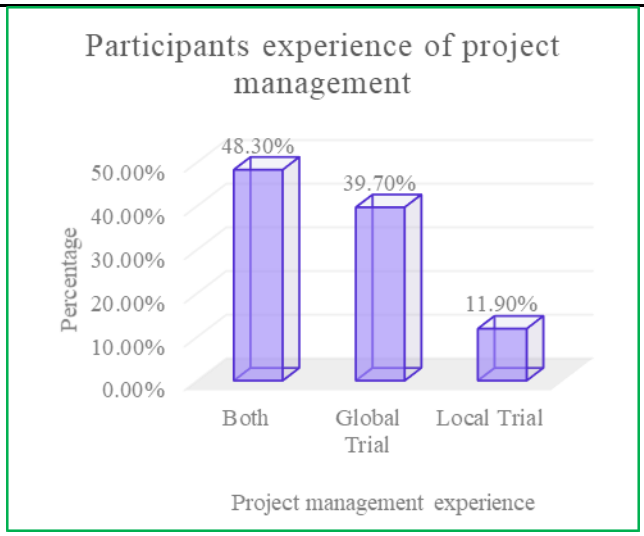

Figure 2

39.7% (203 participants) have experience of working only in the global trial, 11.9% (61 participants) have experience of working only in the local trial and 48.3% (247 participants) have work experiences of both local and global trials.

76.1% (390 respondents) had experience in working with risk-based monitoring while 23.9% (122 respondents) had no previous working experience in RBM. 30.50% (156 participants) have experience of 1-5 years, 33.30% (170 respondents) have 6-10 years of experience, and 12.30% (63 respondents) have 11-15 years of experience in the field. 87.5% (447 respondents) had been working in their current role from 1-5 years, 11% (56 respondents) had been in their current role of from 6 -10 years, and 1.6% (8 respondents) had less than 1 year of experience in their current role.

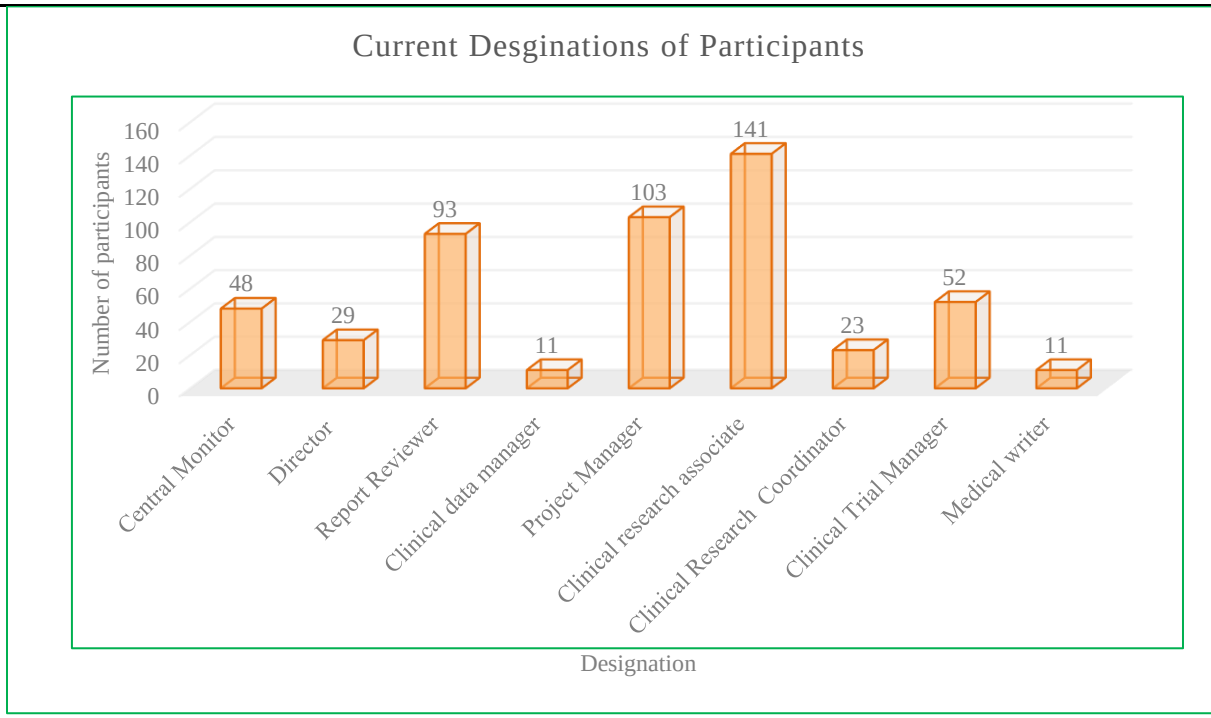

Figure 3

The above figure represents the current designation of the respondent in different organizations at different roles. The majority of the respondents are clinical research associates, Project managers, clinical trial managers, and central monitors including trip report reviewers.

The next question posed to the participants was, 'What parameters are looked into while analyzing the site performance analyzed in real-time management?' 403 respondents (78.86%) said time taken for query resolution. 242 respondents (47.35%) said time from patient visit to CRF entry. 282 respondents (55.18%) said real-time or periodic streaming. 246 respondents (46.28%) said protocol deviation reporting (under or over reporting).

The participants were asked, 'What amongst the below are could be the possible reasons the organization is not ready for RBM implementation?' 334 participants (65.36%) said unable to define critical variables. 253 participants (49.51%) said the trial design is too complex. 216 participants (42.27%) said the trial size is too small. 268 participants (52.44%) said hesitant to change. 210 participants (41.09%) said swapping RBM with remote monitoring.

The next question was, 'What are the steps sponsor shall take to adopt to RBM?' most participants, 80.23%

(410 respondents) said implementing a risk assessment plan. 70.84% (362 respondents) said defining critical data and processes. 77.29% (395 respondents) said creating a quality and risk plan. 62.42% (319 respondents) said developing a study monitoring plan.

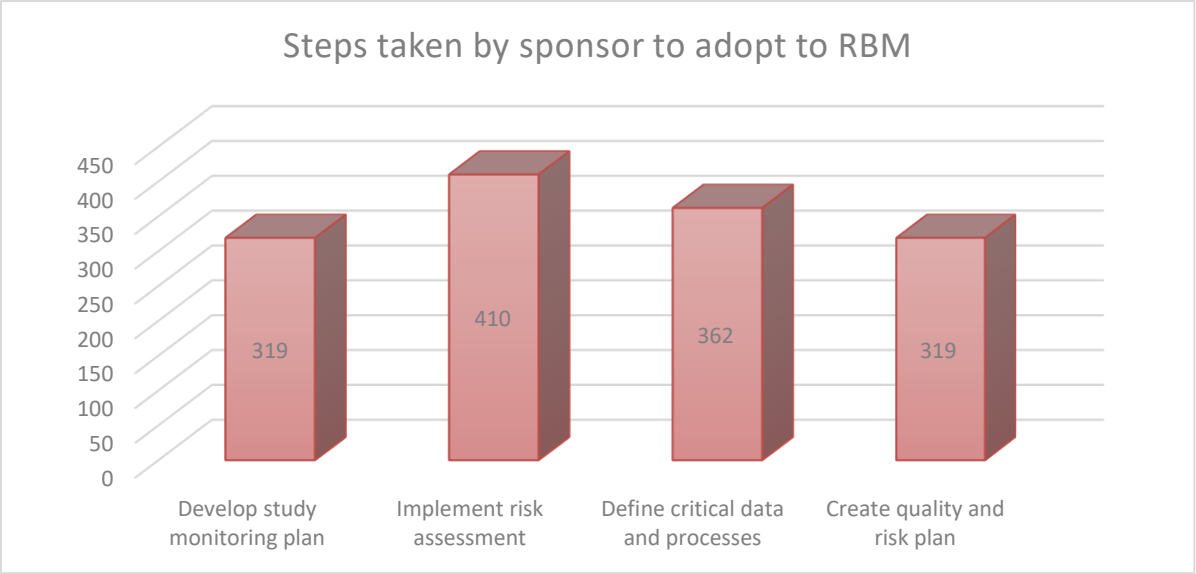

Figure 4

The next question was, 'What amongst the following should be included in the Risk-based monitoring plan for successful output of the RBM model?' 46.77% of the participants (239 respondents) said critical data. 75.53% of the participants (386 respondents) said key risk/quality/performance indicators. 56.36% of the participants (288 respondents) said potential error types and associated remedial actions and action triggers. The participants were asked, 'What according to you, adoption of RBM method can lead to?' next. 81.01% of participants (414 respondents) said early detection of risk. 54.01% of the participants (276 respondents) said a reduction in efforts. 59.09% of the participants (302 respondents) said cost reduction. 76.32% of the participants (390 respondents) said focus on critical data.

The participants were asked, 'Do you think it is important to change protocols and study design to include RBM?'. 40.90% of participants agreed to the statement and 23.09% of the participants strongly agreed. 23.87% of participants neither agreed nor disagreed.

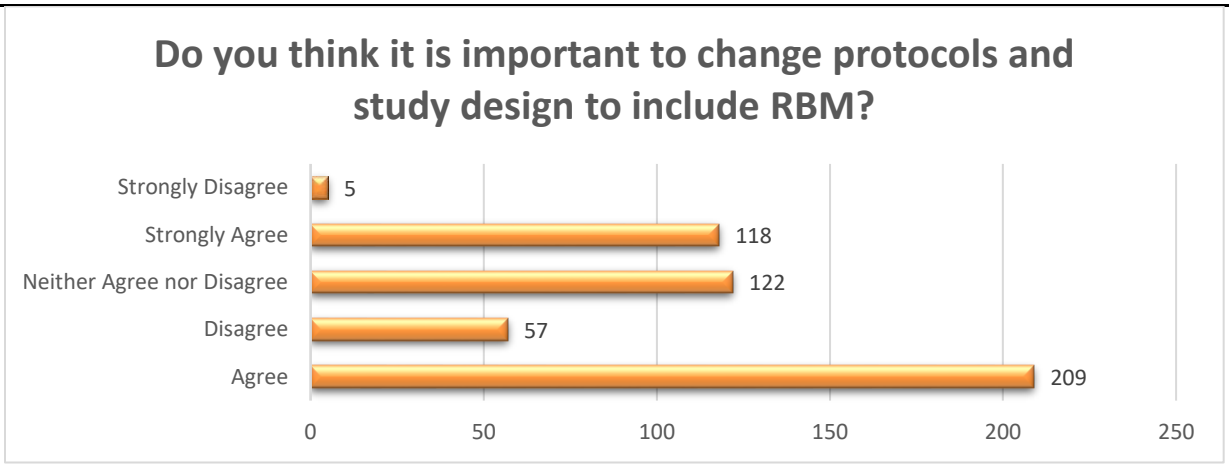

Figure 5

The participants were then asked, 'According to you, which alternative SDV approach would help in the reduction of cost and time management?' 39.13% of participants said mixed SDV, 35.81% of participants said random SDV, 22.89% of the participants said 3-tiered SDV, and 2.15% of participants said declining SDV.

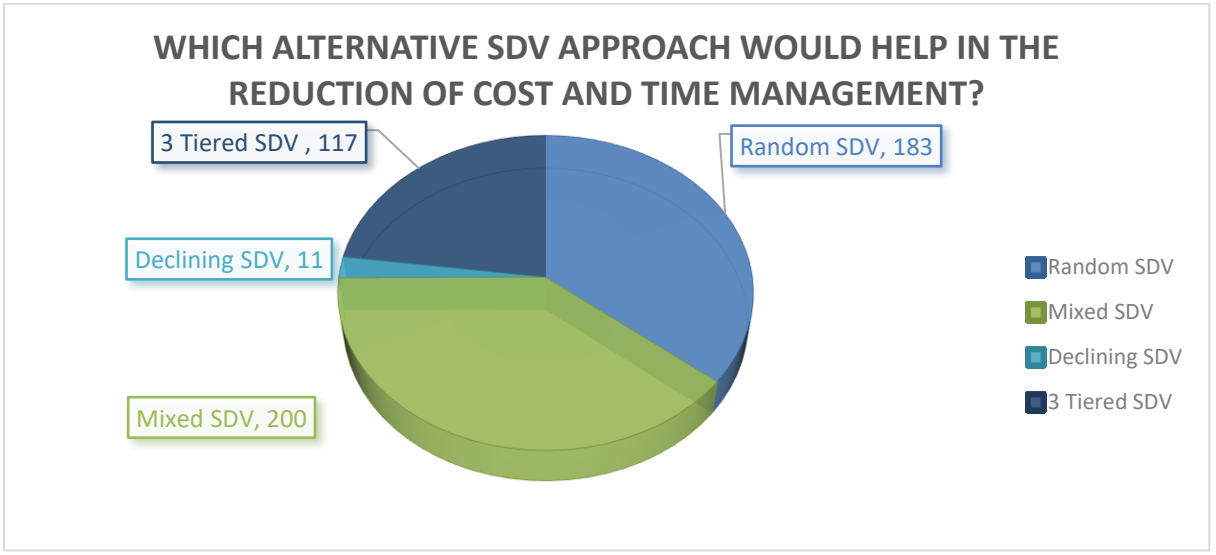

Figure 6

Discussion:

While the industry talks of the successful and effective implementation of the RBM the primary question that is floating around is, what adoption of RBM can lead to; the literature and survey data answers these questions as adoption of RBM can lead to reduction in efforts, early detection of risk, cost reduction, focus on critical

data points, increase in compliance to protocol and collaborative approach. [8]

The RBM not about reduced SDV but focused and targeted monitoring hence alternative SDV approaches like mixed SDV, random SDV 3 tiered SDV can adopted however the literature indicated use of additional alternative SDV approach declining SDV approach which is not the preferred choice in the survey data.[57]

Not only RBM speaks about adaption of alternative SDV approach but also emphasizes on alternative monitoring methods and the analyzed data along with literature) is indicative that review of sites process, procedure, and records and SDV and corroboration are the alternative monitoring methods that can be applied to a clinical trial. The concept of RBM is not new however the concept of implementation of RBM still is relatively new. [9]

The survey data in compliance to published literature suggest that sponsor should select the technologies that are able to examine the baseline risk, supports both the on-site and centralized monitoring techniques, is cost efficient and provides a process for systematic review of the trials risk profile. Subsequently, developing study monitoring plan, defining critical data and processes, developing quality and risk management plan, and implementing risk assessment will help the sponsors to adapt to RBM faster. [10], [8]

The issue management system should follow some basic principles of proactive risk management tracking, single source for all trial roles involved with risk/issues management, tracking the risk at site-, country-, and protocol-level risks/issues, integrates with the aggregation platform, drives global consistency in processes, tools, and nomenclature, and reduces the time and manual effort. The survey data is also indicative that issue management system must follow all the principles that literature suggested. [8]

The success of RBM system will depend on how the risk-based monitoring plan is developed. The risk-based monitoring plan must define critical data points, key risk indicators, key quality indicators, key performance indicators, potential error types and associated remedial actions and action triggers, allowable error rates, initial SDV approach, explains the basis for adjusting the SDV approach during the study and provides the basis for scheduling monitoring visits and adjusting the visit schedule. The survey data is in alignment to the requirements of the risk-based monitoring plan mentioned in the literature. The survey data in compliance with the literature agrees that incorporating quality by design at concept stage improves the protocol design and monitoring plan. It was also evident in the survey results and literature that development of monitoring

plan should consider factors like complexity of study design, types of study end points, clinical complexity of the study population, geographies involved, Relative experience of the clinical indication and of the sponsor with the indication, use of Electronic Data Capture, IP safety profile, stage of study, quantity of data to be collected.[12], [11], [8]

RBM also suggest development of quality management plan as a standalone document that defines the quality parameters and quality tolerance limits. The literature and survey suggested that integrated quality management plan revolves around the following principles that quality is built in from the protocol development and managed through process of continuous improvement, quality goals and metrics are prospectively identified throughout the study duration, and risk to quality are prospectively identified and mitigated.[13]

The literature and survey data also indicated some critical competencies that led to successful RBM implementation which included expertise in clinical development concepts, critical thinking of the team members, thorough knowledge of clinical operations and data management, good communication skills and technical skills, and ability of team members to use the available technologies correctly. Implementing RBM successfully will not ensure that the RBM is used effectively the literature and survey showed effective use of RBM will need personnel's working on the RBM to agree on common terminology, define success criteria, create a RBM process map, define and categorize site risk signals.[14], [15]

Conclusion:

Developing a robust issue management system that is compliant with processes, the other parallel systems in use, use of common nomenclature proves to be a boon for risk-based monitoring model. The issue management system needs to proactively track the identified risk at site, country, study, and protocol levels and manage them thus reducing the time involved in managing risk and the manual efforts. As equipped as the RBM systems would be, we still might not be able to replace the value of people in the conduct of the trials. Although we are still determining how to implement the RBM system, which system works the best, what do we expect from the system. The RBM model has cradled its position within the industry with the support it provided during the pandemic. We can infer that any organizations implementing RBM technologies faces lot of challenges at the initial stage with respect to selection of systems, the management of time, cost, people. However, in the long term the RBM systems prove to be beneficial in reducing the cost, reducing the time

involved and manual efforts.

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