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Research Article

Evaluating the Preliminary Approach of Clinical Research Professional Towards Risk Based Management

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Abstract

Risk Based Monitoring a demand of new era and the need for the hour, which is nothing but a perfectly defined process that assures quality of clinical trials by maintaining its standard by identifying, assessing, monitoring, and reducing the risks which can affect the safety and integrity. The key parameters which would be included under Risk Based Monitoring would include Identify critical data and processes, Perform a risk assessment, Develop a monitoring plan etc.

The study that was conducted was a survey based model and individuals only from the clinical research industry with more than 5 years of experience were allowed to fill up the survey. The received data was analysed using the type I statistical analysis (percentage method) and the results were discussed.

The complete study consisted of more than 85 questions of which four parameters are discussed here i) The first step towards transitioning to RBM approach is change in mind set and a holistic approach. ii) RBM is all about targeted, efficient and intelligent monitoring and e-consenting is an example of intelligent monitoring. iii) Incorporating quality by design at concept stage improves the protocol design and monitoring plan, and iv) As sophisticated as RBM can be and as helpful as they can be, you still cannot replace the value of people being on site. To which it was understood that acceptance towards these parameters is quiet positive from the industry experts, let it be the ones from sponsors or from CRO, With RBM experience or without RBM experience.

Keywords: Risk Based Monitoring; Monitoring Plan; Onsite Monitoring Versus RBM; Approach Towards RBM

Introduction

ICH- GCP defines Monitoring as the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, The Principles of GCP, and the Medicines for Human Use (Clinical Trails) Regulations - where applicable.

Monitoring the clinical trials should be conducted in most effective way is stated by researchers. This led to increase of on-site monitoring visits with 100% data verification.

The integrity of trial data, protection of the rights and well-being of study participants is measured by monitoring activities. The trial site monitor is a member of the trial team and is a link between the sponsor and site study team. Monitoring is an ongoing process conducted before, during and after the trial and is classified in four distinct types of visits (pre-initiation, initiation, routine and close out) [1].

On-site monitoring

The designated site monitor conducts periodic visit by visiting the site, often the site monitors are sponsor employees or

contracted independent monitors depending on the type of trial, or the trial manager for non-commercial trials, or on-boarding local monitors may be beneficial, as they have experience in the local language, culture and practices. It is expected that in an early phase trials, for example first in human studies, 100% source data verification of data is done against the patients source while in late phase trials where less risk is involved, only a certain percentage of participants data may be verified [2].

Remote monitoring

Remote monitoring involves off-site evaluation performed by the monitor away from the site at which the clinical investigation is being conducted.

In Remote monitoring the monitor or clinical research associate (CRA) reviews the data without visiting the investigational site via secure online workspaces or other platforms. The monitor executes the protocol in regular manner and data is recorded in the electronic case report forms (eCRFs). The investigational site staff is expected to upload all the trial related documents such as informed consent forms, source documents, lab reports to online workspace so that, the data can be immediately reviewed by the site monitor. The data entered in eCRF is verified against the source documents available online hence this monitoring visit is termed as remote monitoring visit [2,3].

Centralized monitoring

Sponsor personnel or representatives generally referred to as central monitors conducts Centralized monitoring. Centralized monitoring involves analytical evaluation carried out by central monitors at a central location other than the site at which the clinical investigation is being conducted.

Central monitoring uses analytics and visualization of reviewing aggregate data to identify poor performance of sites, detect trends & patterns at site and patient level, predict potential issues, develop mitigate plans for areas of risk, identify and correct issues in execution of a clinical trial. Central monitoring additionally includes issue management throughout the process in holistic manner [2,4].

Risk based monitoring

Risk based monitoring is the process of assuring that the quality of clinical trials is maintained by identifying, assessing, monitoring, and reducing the risks which could affect the safety of a study.

US Food and Drug Administration (FDA) guidance on RBM describes three steps:

- Identify critical data and processes - In a clinical trial, the Quality of a study data and the safety of the participants in the trial are accurately monitored, for each study sponsor should be aware that elements from the informed consent to eligibility to screening and tracking of adverse event are important.
- Perform a risk assessment - A risk assessment is done to evaluate sources of risk and the effect of study errors on those risks.
- Develop a monitoring plan - According to guidance of FDA's, the monitoring plan should define monitoring methods, responsibilities of the personnel involved in trial conduct, and requirements of trial. Monitoring plan is for everyone involved in monitoring trial for communicating risks and monitoring procedures [5].

Benefits of on-site monitoring

- **Building a relationship:** On site monitoring helps build personal contact with site team. The on-site monitor works as a mediator between investigating site and principal investigator. With good relations at site the monitor can detect the issues and resolve them at a very early stage.
- **Checking of data:** On site monitor while on the onsite monitoring visits reviews and verifies the source data by reconciling the patient file with eCRF data. Apart from that on site monitor verifies if IMP is handled in accordance to protocol. During the visit, the monitor reviews the eligibility and if voluntary consent is obtained, reviews investigational site file for completeness, reviews safety events and follows up on subject enrolment and retention [6].

Introduction to RBM model

In the beginning of the 21st century, the number of clinical trials that were planned increased drastically leading to increase in regulatory submissions. Most of the regulatory authorities across the world, faced challenges in assessing these submissions. Not only the number of clinical trials but also the study design complexities increased, and trials started becoming global involving several countries and hundreds of sites. In this change of landscape the challenge was to maintain effective oversight, data integrity and

protect rights, safety and well-being of the trial subjects. The hindrances were the large geographic dispersion of the study/ies, variable investigator experience, site infrastructure, differences in standard of care, and treatment preferences. The traditional oversight method of regular on-site visits by the clinical research associate (CRA) was becoming quite cumbersome, time, resource, and cost intensive [7].

Benefits of RBM model

Risk-based monitoring is the primary feature of centralized monitoring techniques. There are number of benefits as considered to on-site monitoring:

- **Lesser errors:** In on-site monitoring methods, due to human involvement it is prone to error. Automated reviews facilitate the need for manual intervention which helps uncover errors.
- **Reduced cost:** Use of centralized monitoring, the on-site audits can be limited to study sites which have the most issues thus, reducing the cost of overall monitoring
- **Improved analysis:** Centralized monitoring helps determine outliers and/or unusual patterns in data as the data flows into a central risk dashboard, statistical and graphical checks.
- **Cross-site comparison:** Data between sites to assess performance, identify potential fraudulent data, and/or locate faulty or mis-calibrated equipment
- **More timely results:** A dashboard also makes it possible to identify and resolve issues while the trial is ongoing.
- **Automation:** The potential risk alerts are generated by the RBM technologies using machine learning. The prospective analysis of data collected during the trial conduct helps these technologies identify trends and patterns.
- **Increased patient safety and data quality credibility:** Any issues that are identified at the patient level, site level or study level are notified by the RBM technology to the user. The continuous tracking and analysis of trend information and any time available actionable data enables sponsors to take corrective action in a timely manner, improving the patient safety and data quality.
- **Productive On-Site Monitoring:** Excluding the investigator fees, the largest clinical trial cost is associated with clinical trial monitoring. With RBM predictive analytics, the on-site visits are triggered by study-specific risk thresholds instead of pre-defined schedule leading to reduced but more productive on-site monitoring.
- **Improved Efficiency:** Correctly implemented RBM can help shorten the time taken to clean and evaluate the study data. The RBM technology evaluates the data an ongoing basis which further helps reduce the time from end of study to reporting of study results.
- **Better Compliance:** Regulatory agencies are focusing on more robust credibility of patient safety and data quality. Sponsors who are implementing the RBM technology with traceability and audit capabilities are better-equipped to meet current and emerging regulatory requirements [8,9].

Methodology

The study was conducted using a survey based model, primary aim of the complete was to understand the factors to be considered while implementing the RBM model giving a 360 degree view from the research experts from the clinical research industry.

This publication is one of the sub-set of the complete data received for the survey conducted with Approx. 85 question. The study was conducted amongst 511 experts from the industry and a mix variant was considered i.e. individuals having an experience of working with RBM model as well as the ones who do not, individuals who have been working with CROs as well as the ones who are working directly with sponsors and are managing the clinical trials. The designed questionnaire was validated from the industry leaders before its final execution. The data was captured, cleaned, locked and analysed.

Discussion

The data that was received analysed was from 511 industry experts having a mean experience of 9.5 years, amongst these participants the mean experience of working in RBM model was found to be approximately 4 years (3.78 years). 34.24% of individuals amongst the participating individuals were working at managerial grade or above, this will give us the reliability and robustness of the entire data which we would be discussing further in the article. To understand further distribution of the participants from their experience with RBM and the kind of organization they work with (as per figure 1, Organization Type and RBM Experience), it was observed that majority of the participants i.e. 46.18% were

from CRO and with RBM experience and the lowest observed was 4.11% i.e. individuals from sponsors without RBM experience.

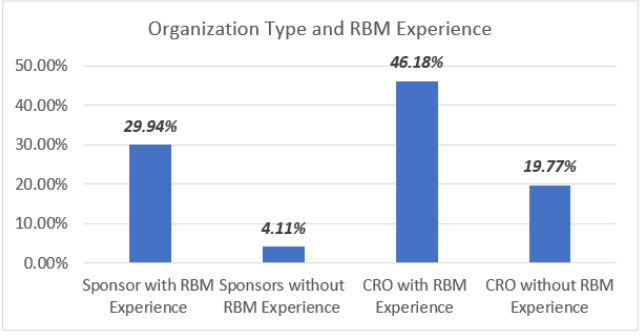

Figure 1: Organization Type and RBM Experience.

Shifting from traditional monitoring to risk-based monitoring technique is a paradigm shift and not all organisations are well adapted to this. There are a few possible scenarios which can be consider before adopting the RBM technique based on the available literature [10,11].

Defining critical variables

The protocol is the guiding document that defines the objectives of the trial, the Inclusion/Exclusion criteria, schedule of events etc. This information ultimately forms the basis of case report forms and the critical variables. While protocol is designed, it is important to emphasize on the objective of the trial since every data point that you collect must support the trial objective.

Size of the trial

Developing the RBM strategies is time consuming hence in case of small trials it will not yield the same results as it would for larger trials.

Complex trial designs

The study design is too complicated; having multiple sub-group population RBM is not a good fit. To implement RBM for complex trials it is best to measure the cost saving and efficiencies of IP before implementing RBM.

Resistance to change

Multidisciplinary team members work together and each has their own objectives. If the different functional team members are not aligned on the benefits of risk based monitoring the organisation may face resistance from them. Hence, identifying the benefits of each stakeholder is essential.

Swapping of risk based monitoring with remote monitoring

The main component of RBM is monitoring critical data points while managing risks. RBM plan may include performance of lesser on-site monitoring visits based on critical points like enrolment, number of deviations etc. However, due to perceived RBM shortcomings sponsors add in remote monitoring, Remote monitoring can prove to be trouble for the site as it needs the site staff to be focused during the call.

Compliance to regulations

Though regulators have published guidance on adapting risk-based monitoring there is no regulatory requirement to implement RBM to all the clinical trials.

Understand the above given scenario of shifting from traditional monitoring to RBM based model, would it be a right shift and the change in mind-set of the industry experts would it be a right approach was strongly agreed on a five pointer scale by approx.. 50% (i.e. 45.60%) it was still agreed by 43.64% which makes it to almost 90% (i.e. 89.24%) of the experts accepting the fact of accepting the shift mentally before its implementation. Detailed in the figure below (Figure 2, Change in mind set of accepting RBM model is the first step to success).

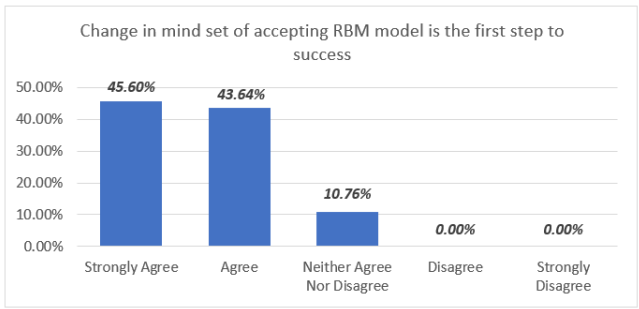

Figure 2: Change in mind set of accepting RBM model is the first step to success.

There are a growing number of RBM technologies being made available, but drug developers should understand that features vary widely from software to software and many fall short from

delivering the full benefits of RBM. Some RBM technologies might only look at risk in isolation, without context or analysis. Some may be limited by their reliance on retrospective data, missing the critical capability to draw insight from emerging issues or placing undue emphasis on irrelevant historical information. An incomplete approach to identify, manage, and analyse risk introduces complexity and cost without adding value. Moreover, a system that fails to fully assess risk could also introduce a new risk: a false sense of security. Sponsors and CROs may mistakenly believe that they are utilizing RBM, without fully benefiting from all that RBM can offer. Hence, we can say that RBM is all about targeted, efficient and intelligent monitoring and e-consenting is an example of intelligent monitoring. When asked to participants it was observed that concept was well accepted by the ones with RBM experience as well as by the ones who were without RBM experience and even there was no change in the mind set between sponsors and CRO personnel (detailed below in figure 3, RBM is all about targeted, efficient and intelligent monitoring) 58.55% of individuals strongly agreed for the quality of RBM of which 42.16% were with RBM experience and 16.39% were without RBM experience, 30.46 were from sponsors side and 38.87 were from CRO side when done a direct comparison. At the same time only 7.83% of total participants did not agree to the quality of RBM.

Figure 3: RBM is all about targeted, efficient and intelligent monitoring.

The well-designed protocol is the most important tool for ensuring human subject protection and high-quality data. A poorly designed and/or unclear protocol may introduce systematic errors despite rigorous monitoring. Additionally, the data quality can be influenced with factors like the complexity of the trial design and the type and amount of data collected [7].

Based on the initial guidance, the FDA proposed a new draft in March 2019 which discusses the importance of identifying critical data and processes, conducting a risk assessment, and developing a monitoring plan specific to the investigation. FDA believes risk-based monitoring is an important tool to allow sponsors to identify and address issues during the conduct of clinical trials.

The monitoring plan is the key aspect of the risk-based monitoring method. Sponsors must consider the following factors while developing the monitoring plan.

The fundamental goal of the monitoring plan is to prevent the expected risk identified during the risk assessment. The elements like type of study, complexity, extent of monitoring, types of study end-points, study population, Investigator experience with the indication and sponsor and vice-versa, use of eCRF, safety of the investigational product, stage of study are important to be considered.

The monitoring plan must be tailored to meet the specificity of the individual study. The plan should describe the monitoring methods, responsibilities and requirements for the trial. The plan should also describe the specific risks that need to be addressed during monitoring. The plan should provide information on the roles and responsibilities of individuals involved in the trial [7].

Understand the importance of Protocol design and Monitoring plan, incorporating a quality by design towards RBM at concept stage will improves the protocol design and monitoring plan to which 87.47% participants agreed with 27% participants strongly agreeing the same. None of the participants of 511 disagreed to this and only 12.52% were not sure as to whether it would work. When directly compared between the individuals with RBM experience to the ones without RBM experience no major difference was observed and similar scenario was on comparison between sponsors personnel and CRO personnel (detailed in figure 4, Incorporating a quality by design of RBM at concept stage improves the protocol design and monitoring plan).

The shift in monitoring practice increases the demand from site personnel. With the decreasing number of on-site visits, CRAs have restricted access to on-site documents. Hence, the workload is shifted on the site personnel since they need to spend more time

Figure 4: Incorporating a quality by design of RBM at concept stage improves the protocol design and monitoring plan.

communicating with CRAs and updating systems. The ex-study coordinators believe that RBM systems increase the responsibility for coordinators to ensure protocol compliance and data collection.

In conventional monitoring, the CRAs were a major support to site staff for most activities however as the CRAs role shifts to a risk assessment role, the study coordinators also see a parallel shift in their responsibilities. With increase in RBM activities the CRAs have to manage the virtual relationship with the site, and have to deal with increased complex issues due to this type of relationship. This sets-up a need for different levels of communication skills for the CRAs [12].

Does this mean that you can replace the value of people being on site? Answer to this question still continues to be NO even after deliberate discussion done above as when the question was asked to participants "As sophisticated as RBM can be and as helpful as they can be, you still cannot replace the value of people being on site". 82.94% participants agreed to the same and there was no major difference of opinion irrespective of their experience with RBM or with the organization they were associated to. Only 1.81% participants disagreed to this.

Figure 5: Cannot replace the value of people being on site.

Conclusion

Shift of mindset is a key to every process and the same was understood from the participating industry experts when they shared their views about the acceptance of RBM and the shift of mind set being the first and foremost parameter for the right shift. When tried to further dive to understand the key concept of RBM model which talks about the targeted, efficient and intelligent monitoring, irrespective of an expert having an experience of RBM or not the primary objective of RBMs was agreeable to majority of the participants. Protocol design and monitoring plan the two key pillars of a successful trial can be designed in a better way if the implementation of RBM is taken into consideration at the concept stage. At the same time, though the appreciation of RBM by all the industry expert continued, still the preference towards the on-site monitoring was still preferred as the majority accepted that the value of people being at site cannot be replaced by RBM.

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