MAR Pathology and Clinical Research (2023) 2:4
Research Article

Understanding the 'Risk' and 'Risk Management' in 'Risk Based Monitoring Model'

Ms. Heema Desai[*1], Dr. Kaushal Kapadia[2]

1. Texila American University.

2 Clinical Research Professional.

[*]**Correspondence to:** Ms. Heema Desai, Texila American University

Received: 01 September 2023

Published: 15 September 2023

DOI:10.1027/marpt.2023.0376

Abstract

The move toward an RBM approach requires change management related to people, process, and technology. Commitment at the leadership level, along with staff training and a clear understanding of each team member's roles and responsibilities, helps ensure that RBM is incorporated into the DNA of both the company and the clinical trial. For an organization to implement RBM they need to primarily understand the organizations requirement in terms of trial complexity, sample size, readiness to change, the selection of the best available technologies, the financial aspect involved, managing quality and risk while implementing systems successfully. Systematic identification of risk and assessment must be carried out after protocol finalization and site selections. This will lead to identification of key risks to be monitored for the study. The identified risk would be related to the process, people, systems, and technology used in the study. Assessment helps to categorize these risks as high/critical, medical, or low risks. This risk categorization influences monitoring aspects, especially extent of onsite monitoring. The research explains how incorporating quality at the very beginning is crucial in managing quality throughout the study. The data collected gives a precise understanding of how implementation of RBM model helped the industry.

Keywords*: Risk, Risk management, RBM model, Risk indicators, Risk mitigation.*

Introduction:

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.

The regulations encourage sponsors to develop monitoring plans that manage identifies risks to human subjects and data quality and address the challenges of oversight. The regulation suggests a risk-based approach to monitoring; however, does not suggest any less vigilance in oversight of clinical investigations. Rather, it focuses sponsor oversight activities on mitigating key risks to data quality and to processes critical to human subject protection and trial integrity.

The risk-based approach is dynamic in nature, more facilitating the trial conduct and oversight. The guidance primarily emphasizes on the processes and procedures needed to ensure clinical trial quality and subject safety. Monitoring works as quality control tool to evaluate if study activities are performed as planned and deficiencies can be identified and corrected. However, monitoring alone does not ensure quality. The regulation proposes a quality risk management approach to clinical trials.

In context to clinical trial, monitoring is used in different ways. Monitoring refers to the assessment of conduct, oversight, and reporting of findings of a clinical trial; evaluation of safety data and benefit-risk ratio an investigational product; and to the monitoring of processes and systems essential to proposing, designing, performing, recording, supervising, reviewing, or reporting clinical investigations in CROs. [1]

In line with the RBM guidance, sponsors should identify and perform a risk assessment on critical data and processes that protects trial subjects. The risk assessment is performed to identify and understand the nature and source of risk. Also, identify the potential causes of risk that can affect the collection of critical data and processes. The risk assessment supports the development of a monitoring plan hence sponsors should document methodologies for risk assessment, conclusions from the risk assessment and how assessment and decisions were made on identified risk. The monitoring plan should include information on how to monitor, manage and mitigate the risk.

A risk-based monitoring approach focuses on oversight activities on preventing or mitigating risks related to quality, including risks to protection of human subjects and data integrity. Monitoring should also focus on less likely risk but can have a significant impact on the data quality. Sponsors must tailor the monitoring activities to address the identified risk. Additionally, the monitoring plans must be flexible to address the issues and risk identified during the conduct of the trial.

Assessing risk involves two steps risk identification and risk evaluation. For system level risk identification, the systems should be analysed to identify potential risk that could affect organization and for project level risk identification, trial specific information should be analysed to identify the risks. Risk evaluation includes establishment of priorities at the time of study design throughout the different stages of the trial. The data collection and monitoring tools should reflect the priorities.

The purpose of Risk control is to reduce the risk to an acceptable level. During risk control, a mitigation plan should be prepared and implemented. The amount of effort used for risk control should be proportional to the significance of the risk and the importance of the process or outcome exposed to identified risk.

Risk mitigation involves actions taken to reduce the unacceptable risk. Unacceptable risk can be defined as the risk that probes considerable impact on subject's safety and rights including the credibility of data. Risk mitigation plan should be project specific and can include protocol design, designing of monitoring plan, audit, and data management plans to identify priorities and risk. Risk mitigation can also include process for identification and escalation of risk.

Risk review mandates the integration of risk assessment and risk control with risk management tools and the communication of the results and data associated to the risk identified and the documentation of the actions needed to mitigate the risk.

The feedback from the risk review should be analyzed and summarized. The analyzed report will include variable measurement, their timing, assessment of deviation and missing data. Additional information can be achieved by well-designed intra and inter site variance analysis on single or multiple variables. Trend Analysis should be done in relation to the overall impact on the scientific benefits and usability of the generated data as established through priority setting and identification of risks and can be supplemented with information on process compliance based on monitoring/data management reports. [2], [3], [4]

The RBM plan must consider the potential issues which might lead to changes in the monitoring activities. Some findings from KRIs, CSM reports during central monitoring would lead to change in the planned

monitoring activities. It is advisable to define in the RBM plan in the beginning regarding these potential events that may lead to change in monitoring plan, especially change in on-site monitoring activities.

Developing an effective RBM plan is very crucial to successful implementation of RBM and to achieve real benefits of RBM. Identifying the right types of risks allowing adequate monitoring of overall study hence, using a good mix of KRIs and CSM reports is very important. RBM plan requires to clearly define the objectives of various monitoring activities, extent, and frequency to monitor those risks. RBM plan should proactively consider the potential events/incidences which might change the monitoring activities at site level. A well-developed RBM plan helps in seamless study management, ensuring high quality data, better monitoring of patient safety, and induces cost efficiencies as well. [5], [6], [7], [8]

Methodology:

This study used a survey method to collect data about the opinions and experiences of the clinical research professionals who have worked on risk-based management systems at some point of time in their clinical research career. The survey is conducted among clinical research professional having more than five years work experience in 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, 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 communications like mail, phone, social media etc. This research is a questionnaire-based survey project targeting to receive the responses from 500 clinical research professionals. For handling such a huge influx of data, an electronic data capture system was built. This study used quantitative methods to collect data.

Results:

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

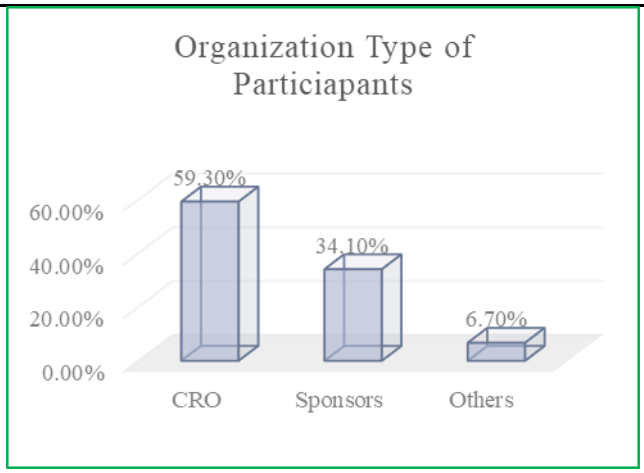

Figure 1

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.

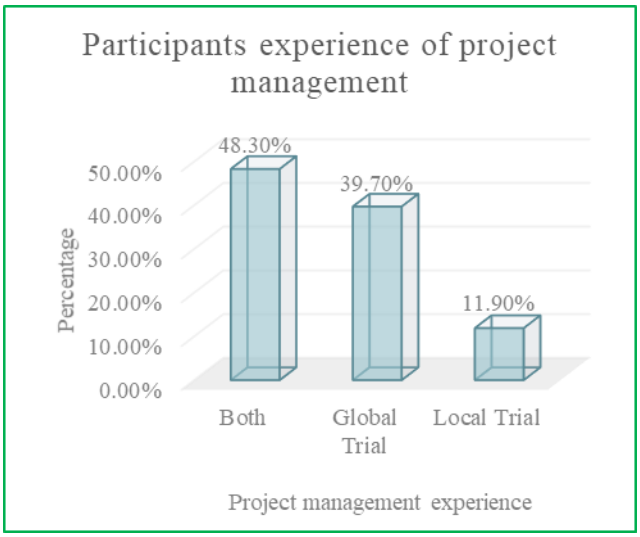

Figure 2

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.

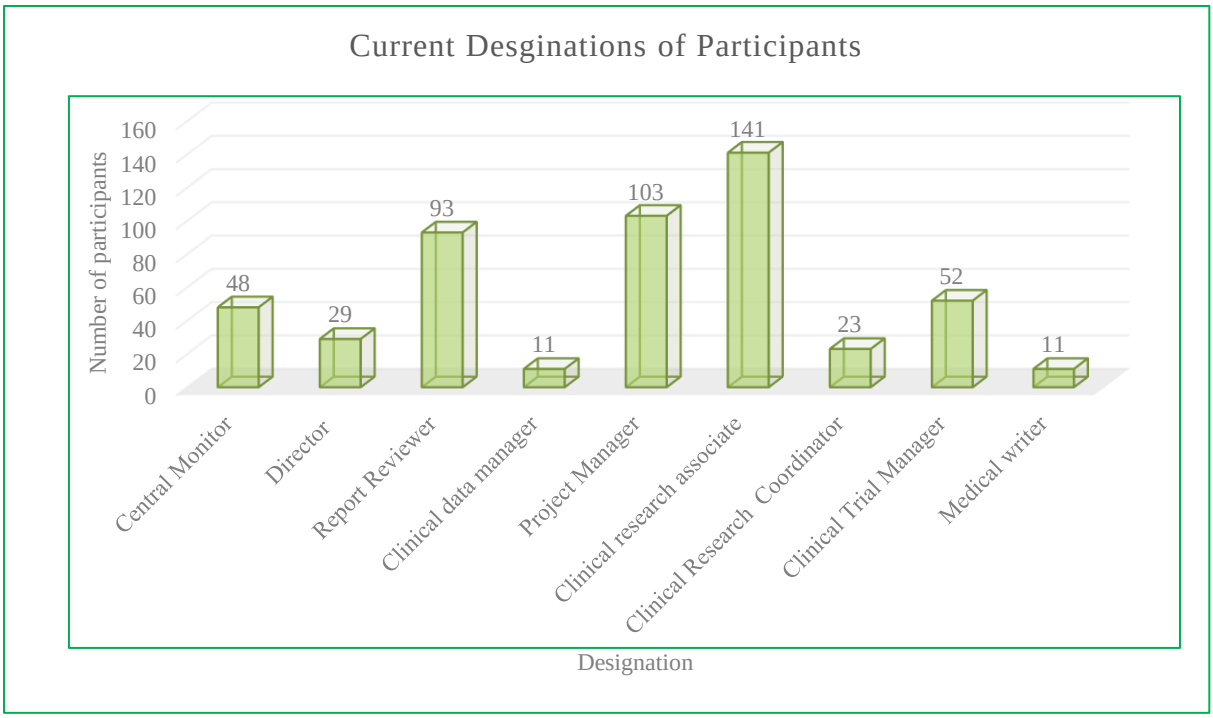

Figure 3

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 participants were asked, 'What are principles followed in the development of issue management system?' Proactive risk management tracking and management, which was the choice of the majority, was selected by 415 (81.21%) of the participants. 60.27% (308) of the participants said single source for all trial roles involved with risk/issues management. 22.50% (115) of the participants said, tracking the risk at site-, country-, and protocol-level risks/issues. 67 participants (13.11%) said drives global consistency in processes, tools, and nomenclature.

The participants were then asked if they agree to the statement, 'The technology frame work must have a flexible yet robust infrastructure and allow for gradual adaptation, both for number of trials and therapeutic areas.' 60.46% (309) of the participants agreed to the statement and 27.20% (139) of the participants strongly

agreed. 9.19% (47) of the participants were neutral on the matter.

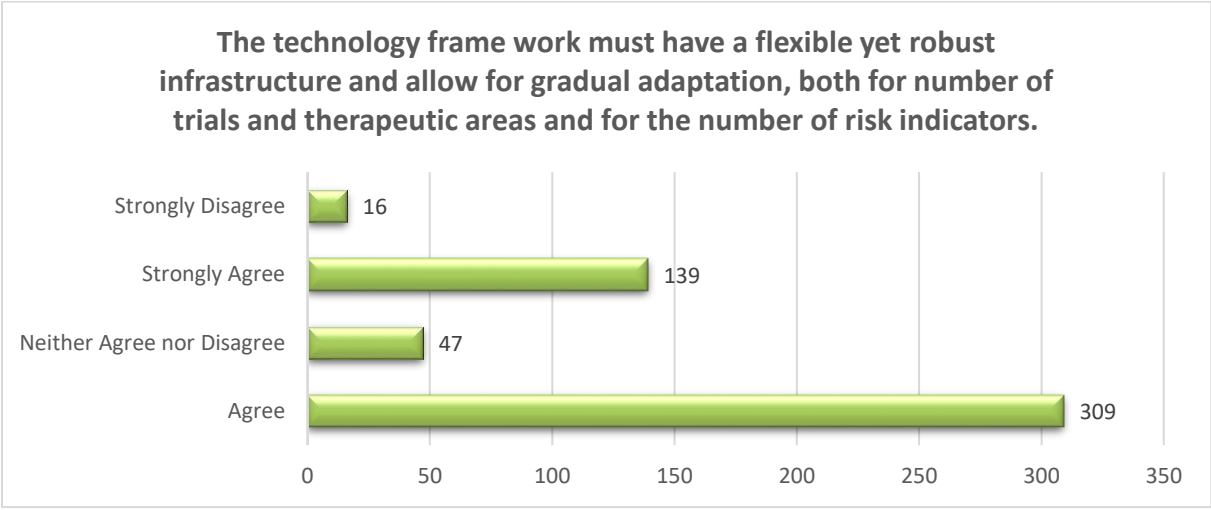

Figure 4

The participants were asked what are the common risk areas according to them since the RBM model is all about proactive risk identification. Over half of the participants (53.03%) said poorly designed protocol is a common risk area. 302 participants (59.09%) said inadequate planning for trail conduct, 422 (82.58%) participants said insufficient planning for risks associated with study population and IP.

'The prime focus of clinical trial is patient safety- who according to you has the best opportunity to mitigate the risk to subject first hand?' was the next question posed to the participants. 35.02% (178) of the participants said IRB/IEC, 36.39% (186) of the participants said, Sponsor, 41.68% (213) of the participants said the site research coordinator, 52.05% (266) of the participants said Study team or safety team and 83.95% (423) of the participants said the investigator.

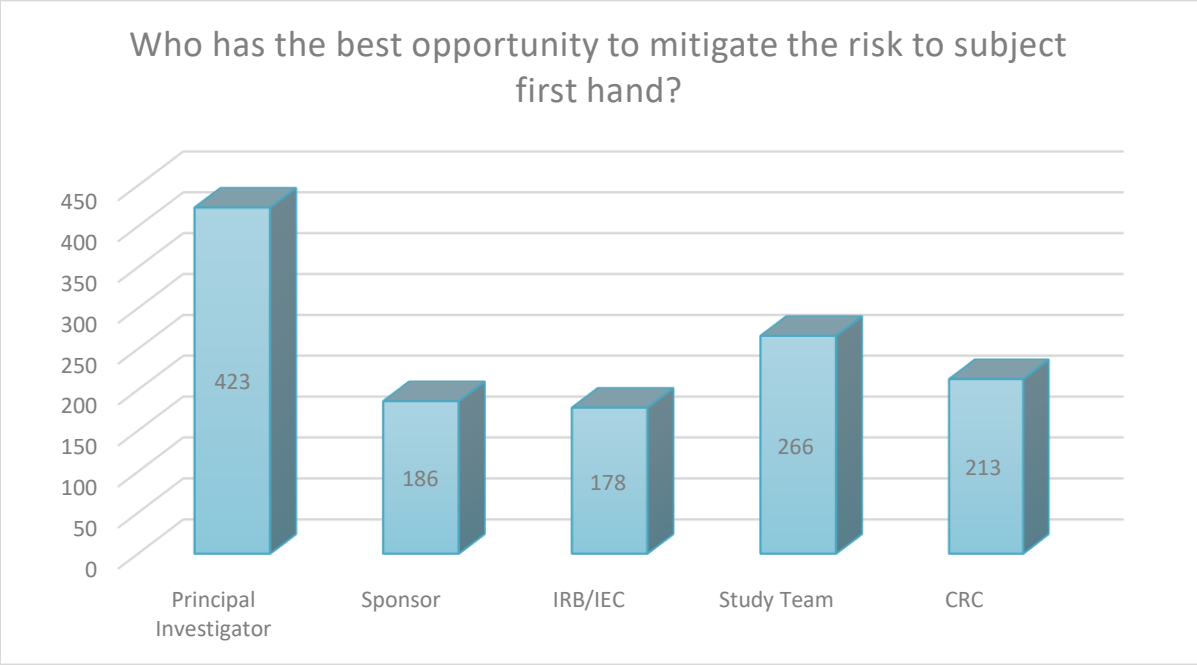

Figure 5

The participants were asked what constitutes as a study-level risk, according to them. 334 participants (65.64%) said study endpoints, subject critically. 48.53% of the participants (248) said no procedures, rate of enrolment, or centers. 43.05% of the participants (220) said study type/ regulatory designation.

They were also asked what would sponsor-level risk include. 82.77% of the participants (423) said regulatory challenges. 319 participants (62.42%) said new technologies. 49.11% (251) of the participants said Stakeholder value in IP.

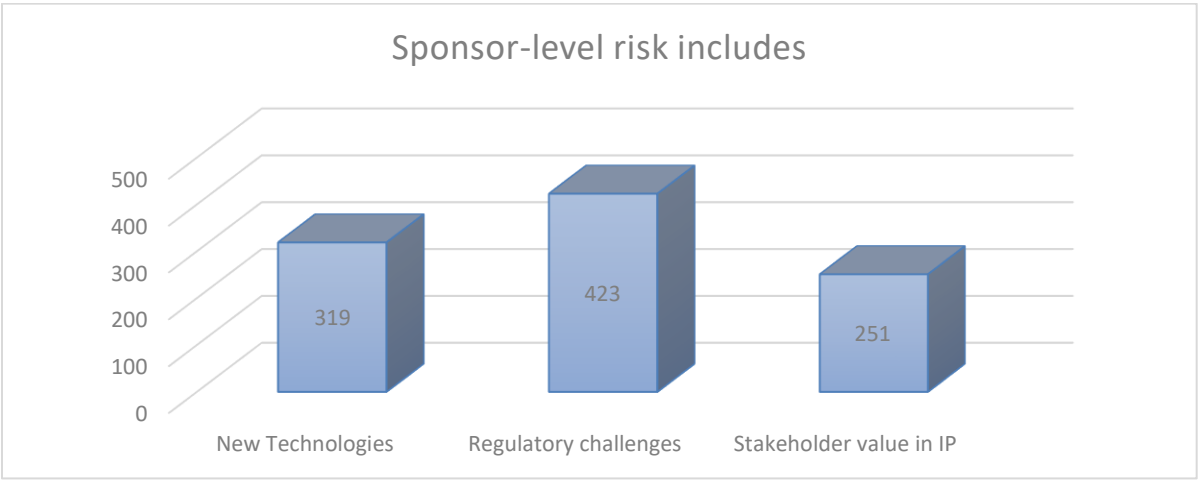

Figure 6

The next question was, 'How can sponsors mitigate clinical trial risk by the implementation of a risk-based approach?' 86.10% of the participants (440) agreed to predict the quality potential prior to SIV. 63.79% of the participants (326) said protocol designing. 53.42% (273) said predict site enrolment. 43.44% of participants (222) said patient retention.

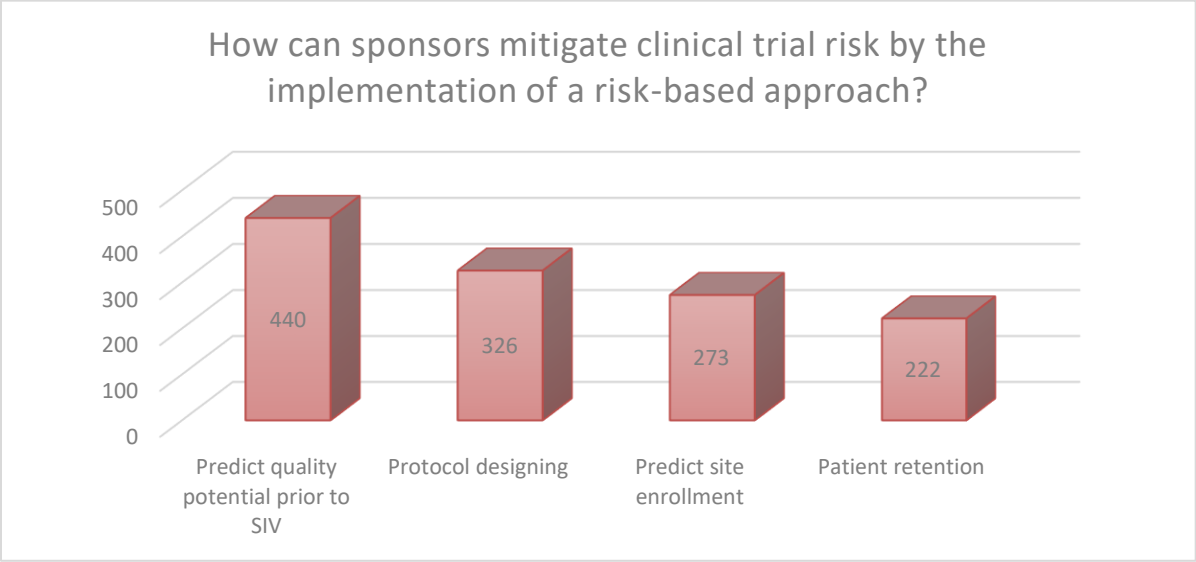

Figure 7

Discussion:

The primary objective of implementing risk-based monitoring model is assessing risk before actually it occurs. The survey data suggests 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. [4], [9]

The primary focus of risk-based monitoring approach is identifying the risk at the initiation and mitigate them before it hampers the data quality and patient safety. The literature suggested that the best opportunity lies with site research coordinator and the PI to mitigate the risk first hand while the study data shows that subject safety can be maintained first hand by the PI , site research coordinator and the monitors however, the overall

responsibility of subject safety lies with all major stakeholders of the clinical study inclusive of; the study team, safety team, the sponsors and the IEC/IRB.[10]

Apart from risk related to the safety the literature outlined multiple other risk like; Number of geographies involved, Investigator experience, sponsor-investigator relationship, use of technology, data quantity to be collected, GCP compliance history of the site, type of the study, study endpoints and criticality, No. of Procedures, rate of enrollment, centres, Product safety profile, Study duration, Design complexity, execution complexity, Stakeholder value in IP, and the Regulatory challenges. The survey data also agrees that these can be the foreseen risk which can be categorized as site-level risk, study-level risk and sponsor-level risk. [10] Both the literature and the survey data indicate that this risk can arise because of poorly designed protocol, insufficient planning for risks associated with study population and IP, inadequate planning for trial conduct, poorly chosen site/investigator, inexperience of site personnel, Lack of sponsor oversight (monitoring, safety). [10]

The literature mentioned that these risks need to be managed and in the RBM model technology needs to be deployed to manage this risk at the initial phase hence systems should allow effective issue management. The issue management system should follow some basic principles of proactive risk management tracking, a 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 the issue management system must follow all the principles that the literature suggested. [9]

The literature also suggested that risks can be mitigated by the implementation of an RBM system which can predict site enrollment, predict quality potential prior to SIV, protocol designing, and patient retention can help mitigate identified risks. The survey data agrees that the system having capabilities of predicting site enrollment, predicting quality potential prior to SIV, protocol design and patient retention will prove to be beneficial in mitigating the risk first-hand.[11]

Further, the literature and survey data agree that the technology system must have a flexible yet robust infrastructure and allow for gradual adaptation, both for the number of trials and therapeutic areas and for the number of risk indicators [10]

Along with the mitigation of identified risks, processes useful for adaptation of conventional practices related to management, monitoring and conduct of the trial should be identified. Risk based quality management is a systematic process implemented to identify, assess, control, communicate and review the risk associated with the clinical trial during its lifecycle.

Implementation of risk-based quality management approaches to clinical trials facilitates better informed decision making and better utilisation of the available resources. The existing quality systems must be appropriately integrated with risk management, and this should be documented. All parties involved are responsible to contribute towards effective risk-based quality management system.

Low performing sites are common and costly. Most of these sites do not enrol a single patient but it can cost very high in initiating, maintaining, and closing the low performing sites. Sponsors can use predictive models against historical site performance to understand factors that affect quality and enrollment outcomes. Understanding site enrollment and quality potential at the initiation will help sponsors to minimize exposures to low performing sites and sponsors will in turn save cost and improve quality.

Clinical trial timelines, budgets and quality outcomes are greatly impacted due to missing clinical data because of subject dropouts. Subject dropouts happen for several reasons like geo-demographics, protocol complexity, subject commitment, education, distance from study site, employment status, physical activity etc. Although there are technologies that focus on patient engagement but not many are successful. Sponsors should use validated technologies like short Messaging Service (SMS) which are cost-effective and known to improve compliance and motivate patients to stay in a trial. [12], [13], [14], [15]

Conclusion:

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. Proactive risk identification in the areas of protocol development, planning of study population and the IP, selection of investigators and/or sites, inexperience site personnel and lack of sponsor oversight. Nevertheless, these risks can be mitigated if attention is focused on prediction of site enrollment targets, designing of protocol in a way that incorporates quality at the initiation, identifies the patient retention methods. Additionally, the vendor oversight by the sponsor plays an important role in RBM

studies. 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.

References

1. Lynn K., Risk-Based Monitoring: Understanding The Future of Clinical Trial Monitoring; cited from https://www.clinicalleader.com/doc/risk-based-monitoring-understanding-the-future-of-clinical-trial-monitoring-0001; cited on 12Dec2021

2. Morrison et al. Monitoring the Quality of Conduct of Clinical Trials: A Survey of Current Practices. Clin Trials.

3.Koreith K. 2011. The high cost and questionable impact of 100% SDV. CenterWatch Monthly 18:1, 15–7

4.Peter M.J.M. Jongen, Cornelis A. van den Bogert, Catharina W.E. van de Laar, Kim Notenboom, Elysée T.M. Hille & Ingrid Hegger (2016) Risk indicator taxonomy for supervision of clinical trials on medicinal products, Current Medical Research and Opinion, 32:7, 1269-1276, DOI: 10.1185/03007995.2016.1170671

5.Barnes S, Katta N, Sanford N, Staigers T, Verish T. Technology considerations to enable the risk-based monitoring methodology. Therapeutic Innovation & Regulatory Science. 2014;48: 536-545.

6.Ray S. Clinical Teams Should Re-Think Risk-Based Monitoring Costs to Improve Their Bottom Line. Accessed at: http://www.cuttingedgeinfo.com/2013/risk-based-monitoring-costs/

7.Clinical trial delays: America's patient recruitment dilemma July 19, 2014. Accessible at: http://www.drugdevelopment-technology.com/features/featureclinical-trial-patient-recruitment/

8.Boutwell D. Get better at managing clinical trial financials. Pharmaceutical Commerce. June 30, 2015. Accessible at: http://pharmaceuticalcommerce.com/clinical-operations/get-better-at-managing-clinical-trial-financials/

9.RBM Interactive guide; available on https://www.transceleratebiopharmainc.com/rbminteractiveguide/what-is-risk-based-monitoring-rbm/introduction/ ;accessed on 13 Jan 2020

10.Oleson, Kimberly & Fay, Margaret. (2013). Fay MF and Oleson K. A Rationale for a Risk-Based Approach to Clinical Trial Conduct and Monitoring Practices. The Monitor. 2013;12: 9-14. The Monitor. 12. 9-14. Cited on 17 Oct 2021

11.RbM Guidance Document: Ten Burning Questions about Risk-Based Study Management; Moe Alsumidaie, Johanna Schenk, MD, Peter Schiemann, PhD, Beat Widler, PhD, Artem Andrianov, PhD, María Proupín-Pérez, PhD available on: https://www.appliedclinicaltrialsonline.com/view/rbm-guidance-document-ten-burning-questions-about-risk-based-study-management; cited on 4Oct2020

12.Linkov I, Satterstrom FK, Kiker G, et al. 2006. From comparative risk assessment to multicriteria decision analysis and adaptive management: recent developments and applications. Environment International 32: 1072–3.; accessed on 17 Oct 2020.

13.Morrison B, Cochran C, White JU, et al. 2011. Monitoring the quality of conduct of clinical trials. Clinical Trials 8: 342–9.9. Broseteanu O, Houben P, Ihrig K, et al. 2009.; accessed on 17 Oct 2020.

14.Risk analysis and risk adapted on-site monitoring in noncommercial clinical trials. Clinical Trials 6: 585–96.; accessed on 17 Oct 2020.

15.Miseta E. Clinical Leader. June 5, 2019; Balance Capital And Labor For Successful RBM Implementation, available on https://www.clinicalleader.com/doc/balance-capital-and-labor-for-successful-rbm-implementation-0001; accessed on 05 Oct 2020.