Review Article

# Navigating Clinical Trials in India: A Comparative Review of Traditional and Risk-Based Monitoring Approach

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**ABSTRACT**

Clinical research plays a paramount role in expanding medical science, warranting the safety of new treatments, in addition to shaping health-care globally. Verifying that the rights and welfare of study participants are safeguarded and that the reported trial data are accurate, complete, and verifiable from original records, along with ensuring the trial is being conducted in accordance with the currently authorized protocol(s) or amendment(s), GCP, and the relevant regulatory need are all vital parts of monitoring. Frequent on-site visits by monitors to clinical trial locations are part of the traditional monitoring method. Monitors thoroughly examine source papers, confirm the veracity of the data, and guarantee protocol obedience. On the other hand, the goal of the risk-based monitoring (RBM) strategy is to distribute monitoring resources according to risks that have been recognized and important data points. Both strategies will be important as clinical research develops and will necessitate careful thought and adaptation to the unique requirements of each study. Understanding ICH-GCP, USFDA, CDSCO, and other regulatory expectations for monitoring and data integrity is crucial when selecting an appropriate monitoring approach. As the landscape of clinical research continues to evolve, both approaches will play crucial roles, requiring careful consideration and adaptation to the specific needs of each study.

**Keywords:** Traditional monitoring, Risk-based monitoring (RBM), Centralized monitoring, Remote monitoring, Clinical research.

## INTRODUCTION

Clinical research has had a lengthy but intriguing history. Clinical trials have a documented history that dates back to 500-BC's biblical sorts. Efforts were undertaken to improve the design and statistical components of clinical trials later the fundamental tactic was outlined in the 18th century. Changes in the regulatory and ethical framework came next. Clinical trials in India have a rich history dating back to the early 20th century. Regulatory frameworks, such as the Drug and Cosmetics Act and Rules and Indian GCP, have evolved to oversee trials. Clinical research contributes a focal starring role in progressing medical-science, defending the safety of unfamiliar treatments, and shaping health-care worldwide.[1] Clinical trials represent the vanguard of medical progress, heralding breakthroughs in healthcare and pioneering treatments for ailments that were once deemed incurable. Within the vibrant landscape of India's healthcare sector, these trials serve as crucibles of innovation and hope, fostering collaboration between researchers, healthcare providers, and patients. India has emerged as a prominent hub for clinical research due to its diverse population and cost-effective environment. However, as the clinical trial ecosystem grows increasingly complex, the methods employed to monitor and ensure the integrity of these trials become paramount. In the realm of clinical research and trials, monitoring plays a pivotal role in ensuring the integrity and reliability of collected data, guaranteeing research quality and subject safety in accordance with regulatory standards. It is an erudite, invention-based approach to retaining a business's info, granting for improved-informed conclusions concerning wherever and exactly how to assign assets.[2, 3] ICH-E6 (R2) outlines 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, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement*." [4]

In order to monitor trials in India, regulatory structures like the Drug and Cosmetics Act and the Central Drugs Standard Control Organization (CDSCO) have developed. India has grown into a popular place for clinical research as a result of globalization, demanding strict monitoring procedures. According to regulations like 21 CFR 312.50 and 812.40, sponsors are obligated to assure adequate research monitoring and to choose monitors who are qualified to do so based on their training and expertise. Regulators don't specify how sponsors must carry out this monitoring, therefore it might be done on-site, remotely, or through centralized monitoring techniques. Sponsors can implement monitoring procedures that are suitable for specific research using a systematic, prioritized, risk-based approach. Every clinical trial requires a different monitoring strategy, which is neither acceptable nor essential. As a result, the level and kind of monitoring may differ. Each sponsor should create a monitoring strategy that is specific to the trial's risks. Monitoring efforts should

generally be directed on eliminating or reducing significant and probable motives for mistake in the conduct, collecting, and reporting of crucial data and procedures required for subject protection and trial integrity. [5]

Over the years, two distinct monitoring approaches have emerged that are traditional monitoring model and the risk-based monitoring (RBM) model. In the Indian clinical research landscape, understanding the nuances of these approaches is vital for effective trial management and regulatory compliance. The traditional monitoring approach involves on-site visits to monitor every aspect of a clinical trial. This technique has been the gold standard for periods, confirming precise supervision. Nevertheless, it can be resource-rigorous, time-arduous, and moreover may not realistically tackle areas of extensive gambling. Whereas Risk-Based Monitoring (RBM) is a strategic systemic quality management approach wherein sponsor oversight focuses on risk identification, evaluation, control, review, and reporting of key risks, which would directly impact data integrity and subject safety by leveraging centralized monitoring, predictive analytics, and technological advances. It employs a risk assessment to determine the level of monitoring required for different trial components. RBM offers cost-efficiency and flexibility, allowing for more targeted oversight.[6, 7, 8] In a rapidly evolving field, finding the right balance between control and flexibility is essential. Traditional monitoring provides a structured framework, while RBM offers adaptability to trial dynamics. A hybrid tactic that mixes degrees of both standards may be the fundamental to tackling India's distinctive contests.

**TRADITIONAL MONITORING APPROACH:**

The traditional monitoring approach has been the bedrock of clinical trial oversight for decades. However, the landscape of clinical research has evolved dramatically since the inception of this traditional monitoring approach. The traditional monitoring approach involves regular on-site visits by monitors to clinical trial sites. The International Conference of Harmonization Good Clinical Practice (ICH GCP) provides guidance for the monitoring of the conduct of a clinical trial, to verify that reported data are accurate, complete, and accounted for by source records. The regulation states that in widespread there is a necessity for on-site supervising earlier, throughout then ahead of the trial, excluding the nature as well as the level of on-site monitoring have certainly not been itemised by the regulatory interventions or the ICH-GCP. [4]

Monitors meticulously review source documents, verify data accuracy and ensure protocol adherence. This methodology offers a shaped as well as logical method for quality-control moreover data authentication. Historically, this approach has offered a reassuring and comprehensive means of ensuring patient safety and data accuracy. During these monitoring visits, clinical research associates (CRAs) engage in detailed inspections of trial sites, reviewing patient records, confirming data accuracy, and monitoring compliance with Good Clinical Practice (GCP) guidelines. This meticulous oversight, while resource-intensive, has provided a sense of security and confidence in the integrity of clinical trial data. A monitoring report should be given to the site by the monitor following the monitoring visit and stored in the trial master file (TMF). The document will include a summary of actions, developments, difficulties, and pressing problems. However, it can be resource-intensive and less adaptable to emerging issues. Traditional monitoring, likewise, referred to as conventional monitoring, involves a comprehensive and systematic approach to overseeing and ensuring the quality and integrity of clinical trial data.[9-11]

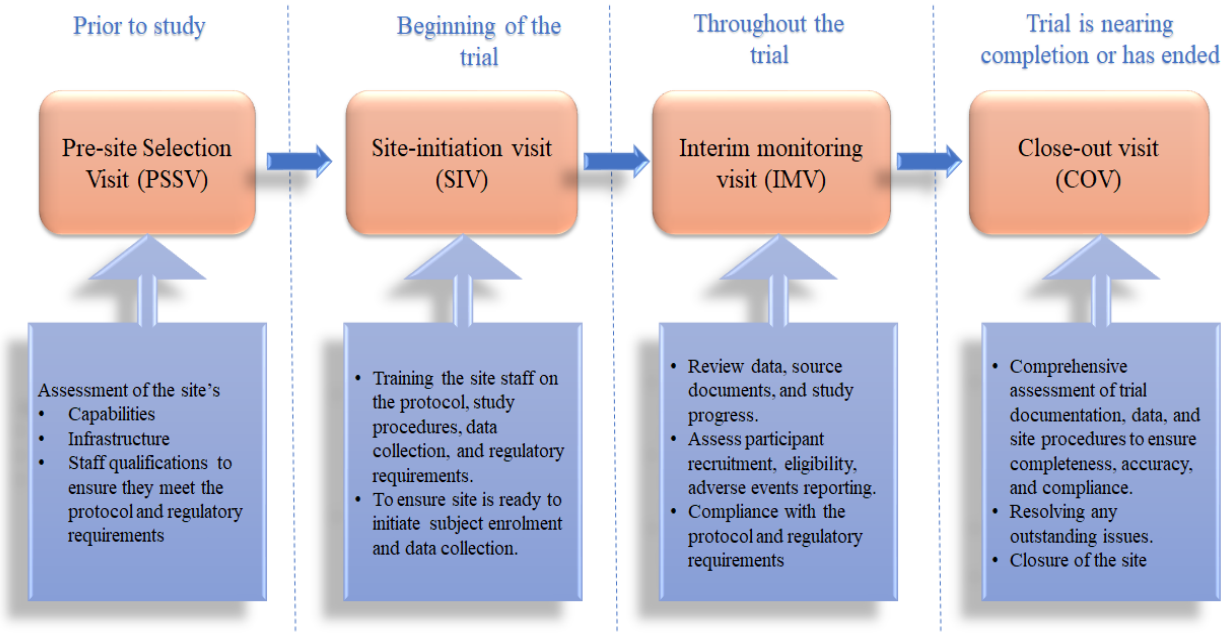


**Figure 1:** Types of Traditional Monitoring Visits

Trials are conducted all over the globe using on-site monitoring, even though the methods utilized vary widely and the practice is not well supported by research. Figure 1 classifies types of traditional monitoring visits in a clinical trial. [12] To provide compelling evidence for the importance of site visits to trial performance and quality, these on-site monitoring measures, including costs, must be experimentally examined. To confirm that the patients signed the contract voluntarily, the monitor may even match their signatures to those on other papers. To confirm that no investigation operations were carried out without prior approval, the monitor can also compare operational documentation like case report form (CRF), adverse event reporting, and drug management records to the dates along with timings of other test findings. To make sure that the actions were carried out in accordance with government, state, and local regulations, monitors can look at how the informed consent procedure with investigators works as well as any supplementary consenting source paperwork. [6, 13]

Additionally, the monitor may thoroughly review every healthcare record, both paper-based and digital, to ensure that every patient satisfies the requirements for participation or disqualification. The monitor can vouch for the site's compliance with federal legislation, institutional Ethics Committee (IEC) approval, and the acquisition of all required paperwork for the research while reviewing legislative documentation. With onsite monitoring, a comprehensive document inventory may be finished, lost or missing papers can be found, and regulatory paperwork can be restructured. The monitor can also assess how well the local research personnel is familiar with the study agreements and institutional ethics committee (IEC) regulations. [9, 14] The key features of traditional monitoring include, 100% Source Data Verification (SDV), Frequent On-Site Visits including fixed schedule.

a. **Source Data Verification (SDV):** One of the hallmark features of traditional monitoring is the practice of 100% Source Data Verification (SDV). This means that monitors or clinical research associates (CRAs) meticulously check every data point in the clinical trial, comparing it with the source documents. Source documents include medical records, lab reports, and other original records created during the course of patient care. The advantage of this aspect is the prominent level of data accuracy and reliability it offers. By cross-referencing every single data point among the source, blunders, as well as discrepancies, can be recognized and assessed promptly, ensuring data quality. However, this approach is resource-intensive as well as time-consuming. It requires CRAs to make frequent site visits and spend substantial time at each site. This can lead to increased trial costs and potential delays. Though it aims to ensure data accuracy but can be recognised as less efficient in terms of cost and time.[15]

b. **Frequent On-Site Visits:** Traditional monitoring adheres to a fixed schedule for on-site visits to review documents, answer site staff questions, and ensure compliance with the study protocol, regulatory requirements, and Good Clinical Practice (GCP) guidelines. This schedule is often predetermined and may not be flexible based on the evolving needs of the trial. For major efficacy trials, corporations normally perform on-site monitoring visits at approximately 8-4-workweek interims. As CRAs visit sites on a pre-established timetable, regardless of whether there are urgent issues or deviations, a fixed schedule provides a structured framework for monitoring activities, ensuring that all trial sites receive regular attention. This predictability can help with planning and resource allocation. The rigid schedule may not align with the dynamic nature of clinical trials. Emergencies, deviations, or issues at specific sites may require immediate attention, and the fixed schedule can hinder the ability to respond promptly. [16]

Traditional monitoring follows a systematic and pre-defined process, making it easier to plan and execute monitoring activities. This structured approach can lead to uniformity in monitoring processes and followed by consistent data collection and reporting across different sites and studies. Since the monitoring activities are standardized, it's easier to estimate the associated costs. Along with these benefits, conventional monitoring is also in line with previous regulatory standards, which is more comfortable for regulatory agencies. Apart from those advantages traditional monitoring shows some cons like resource intensive monitoring, less focus on critical data, and limited adaptability. As traditional monitoring involves frequent on-site visits, which can be time-consuming and costly for both sponsors and sites. Also, the same level of attention is given to all data points, which can lead to overlooking critical data discrepancies; and this approach may not be as responsive to emerging issues or variations in site performance. [17]

**RISK-BASED MONITORING APPROACH:**

Until recently, the typical method for clinical monitoring at a site consisted of routine on-site visits at a set frequency applied consistently across sites regardless of their level of risk and mainly depending on source data verification (SDV) as a mechanism to assure data quality as well as safety for participants. However, there is growing evidence that SDV is far less effective compared to first believed. [14] Risk-based monitoring (RBM) represents a paradigm shift in clinical trial oversight. It acknowledges that not all aspects of a trial carry equal risk and that resources should be directed where they are most needed. This approach is particularly relevant in India's diverse and complex clinical trial landscape. RBM leverages data-driven insights and risk assessments to tailor monitoring activities to the most critical aspects of the trial, focusing on endpoints and patient safety, data integrity, and protocol adherence. This approach seeks to optimize resource utilization while

maintaining the highest standards of quality. RBM introduces the concept of centralized monitoring, which relies on technology and statistical methodologies to identify anomalies and potential issues within the trial data. By harnessing the power of data analytics and remote monitoring, RBM allows for early detection of deviations, reducing the need for frequent site visits and SDV. This approach is especially appealing in the context of India's vast and diverse geographical landscape, where site visits can be logistically challenging and resource-intensive.

Risk-based monitoring is a more targeted and efficient approach to overseeing clinical trials. It focuses on identifying and managing risks that could impact patient safety, data quality, and trial integrity. This method acknowledges that not all data points, processes, or sites carry the same level of risk. The key features of risk-based monitoring comprise Risk Assessment, Centralized Monitoring, Targeted Monitoring, and Remote Monitoring. The efficiency of risk-based monitoring with a conventional monitoring system and conventional on-site monitoring were studied by Osamu Yamada et al. This study concluded that "remote risk-based monitoring may detect critical information along with operational errors as well as traditional or on-site monitoring with 100% source data verification, decreasing visit duration as well as monitoring expense. An efficient substitute for the conventional on-site monitoring of clinical trials is remote risk-based monitoring. Sponsor should consider optimizing use of technologies such as risk-based monitoring to maintain oversight of clinical sites. These technologies can ensure that the trial participant's safety and trial data quality and integrity are being closely monitored. [18, 19, 20]

a. **Risk Assessment:** Prior to the trial beginning, a comprehensive risk assessment is performed to distinguish potential possibilities associated with the trial, such as complex procedures, vulnerable patient populations, plus critical endpoints. The foundation of RBM lies in conducting a thorough and systematic risk assessment at the outset of a clinical trial. This assessment aims to relate potential risks and challenges that could affect the integrity of the trial data, patient safety, as well as the achievement of study objectives. Recognized risks are typically classified into high, medium, or low risk based on their potential impression on the trial. Risks can stem from a range of circumstances, involving the intricacy of the investigational product, the patient population, data quality concerns, and site-specific concerns. In risk-based monitoring Key Risk Indicators (KRIs) play very pivotal role; KRIs are the measures of error rates and data quality that are designated as important for management of the current study. KRIs are critical data and other study variables or operational data that can detect potential issues at site, or trial levels. [19, 21]

b. **Centralized Monitoring:** Unlike traditional monitoring, which relies heavily on frequent on-site visits, RBM emphasizes centralized monitoring. Centralized monitoring leverages technology and data analytics to continuously assess and analyze trial data remotely. A distant, central location is used for the assessment of patient data from several research locations or patient populations as part of centralized monitoring. Site monitors, data managers, and biostatisticians carry out centralized monitoring. Examples of centralized monitoring include reviewing patient laboratory findings, inspecting clinical record documentation at a central office, and panel evaluation of clinical data by a third party for quality assurance purposes or for regulatory submission. [22] This approach enables the identification of trends, anomalies, and potential issues across multiple trial sites in real-time. RBM leverages technology, data management systems, and specialized software to facilitate centralized data monitoring. These tools provide real-time access to data, allowing for more efficient and comprehensive oversight. In this method Statistical tools and data analytics are used to analyze trial data centrally, identifying trends, anomalies, and potential issues without the need for frequent on-site visits. [23]

c. **Targeted Monitoring:** The on-site portion of risk-based monitoring known as targeted monitoring concentrates on the elements of clinical research that have the greatest propensity to affect the safety of subjects along with the credibility of the study's findings. Monitoring activities are focused on areas with higher risks, ensuring that critical data points are accurately captured. This might involve more intense monitoring for high-risk sites and critical endpoints. [24]

d. **Remote Monitoring:** It is a cloud-based remote monitoring system that does not require site-specific infrastructure for remote monitoring since it can be downloaded onto electronic devices as an application and involves the upload of photographs (scanned copies). The source papers, clinical laboratory reports, informed consent forms, and other trial-related paperwork are all moved to a secure online workplace. So that the CRA may quickly access the data anytime it's required. After the data has been uploaded, CRA checks the data from the eCRF with the data from the source document, which is known as a monitoring visit. This is referred to as remote-based monitoring since the source data verification is being done remotely. Remote monitoring principally concentrating on risk objects that could lead to critical data as well as operational oversights. By utilizing technology to remotely monitor and review trial data, reducing the need for frequent on-site visits. This includes data review, query management, and real-time oversight. [3, 25]

Risk-based monitoring approach can be said to be better than traditional one as it shows some more pros over traditional monitoring. Risk-based monitoring prioritizes critical data and areas of higher risk, which can enhance patient safety and data integrity. By concentrating

resources where they are needed most, risk-based monitoring can lead to more efficient use of time and budget. This model is designed to identify and respond to risks and issues as they arise, allowing for greater flexibility in monitoring strategies. By identifying and addressing issues early, risk-based monitoring can lead to improved overall study quality.

Risk based monitoring also shows some cons like complex implementation, regulatory uncertainty, lack of standardization, and it needs some data analysis skills. Setting up a risk-based monitoring system requires careful planning, data analysis, and decision-making processes which makes its implementation complex. Depending on the jurisdiction, regulatory authorities may have varying levels of acceptance and familiarity with risk-based monitoring approaches, so it shows some regulatory uncertainties. Effective risk-based monitoring requires the ability to analyze complex data to identify trends and potential risks, so it requires personnels or technologies with high data analysis skills. Since risk-based monitoring approaches can vary based on study characteristics and risks, there might be a lack of standardization across studies.

**IMPLEMENTATION CHALLENGES IN INDIA:**

While both monitoring approaches have their merits, the Indian clinical research environment presents unique challenges. Limited infrastructure, variable site capabilities, and diverse patient populations require careful consideration when implementing monitoring strategies. Cultural and regulatory factors also influence the choice between traditional and RBM models. With guidance and mandate from regulatory authorities and recent inclusion in ICH E6 (R2) revision, RBM will eventually become a need to change a way of life. As change is disruptive and challenging to manage, implementing RBM in India presents its own set of challenges; however, it stimulates thinking to find solutions. The transition from the well-established traditional monitoring approach to RBM requires a paradigm shift in the mindset of stakeholders, including sponsors, clinical research organizations (CROs), and regulatory authorities. Resistance to change, lack of awareness, and the need for specialized training are common hurdles faced during this transition. The most important action at an organizational level would be to take the involved stakeholders through change management training and ensure that true interdisciplinary coordination occurs on an ongoing basis within the sponsor and CRO organizations. Additionally, data privacy and security concerns must be carefully addressed, as centralized monitoring relies on data sharing and analytics. India's evolving data protection laws and regulations further complicate this aspect of RBM implementation. Guaranteeing that RBM is conducted in a manner submissive to local along with intercontinental regulations is crucial to its success. [8]

**REGULATORY LANDSCAPE:**

The Central Drugs Standard Control Organization (CDSCO) in India governs clinical trials. Understanding CDSCO's expectations for monitoring and data integrity is crucial when selecting an appropriate monitoring approach. Recent updates to regulatory guidelines have encouraged the adoption of risk-based monitoring to align with international best practices. The regulatory framework governing clinical trials in India has undergone significant revisions in recent years. The introduction of the New Drugs and Clinical Trials Rules in 2019 aimed to streamline and expedite the approval process for clinical trials. These rules introduced a risk-based approach to ethics committee review and clearance, aligning with the principles of RBM. Furthermore, India has adopted international standards such as ICH-GCP, which emphasize the importance of risk-based quality management in clinical trials. This alignment with global best practices encourages the adoption of RBM as a means to improve trial efficiency and data quality while maintaining patient safety. The use of this strategy, nevertheless, has been optional. The USFDA published a recommendation on risk-based monitoring in August 2013. The policy established the groundwork for implementing adaptive monitoring using a risk-based strategy that upended the conventional monitoring strategy. This recommendation focused on increasing technological use and using centralized monitoring tools and procedures to oversee clinical trial locations. In this ever-evolving landscape of regulations, understanding the nuances and implications of RBM is critical for sponsors and CROs operating in India. Balancing compliance with innovation is an ongoing challenge that requires a nuanced approach. [26, 27, 28]

## CONCLUSION

The preference between traditional monitoring and risk-based monitoring approaches in clinical trials signifies a pivotal judgment that impacts data quality, patient safety, as well as resource consumption. Traditional monitoring's structured methodology offers consistency and regulatory alignment but comes at the cost of being resource-intensive and potentially missing critical data discrepancies. However, it comes with significant resource demands, entering time, personnel, in addition, travel expenditures. As clinical trial landscapes go forward, there is an expanding recognition of the necessity for more efficient along with cost-effective monitoring approaches. On the other hand, risk-based monitoring (RBM) symbolizes a significant shift in clinical trial oversight, moving away from the resource-intensive, one-size-fits-all tactic of traditional monitoring. The risk-based monitoring approach establishes a more directed and adaptable strategy, aiming at higher-risk areas and admitting for more efficient resource provision. While risk-based monitoring may entail complexities in implementation and potential regulatory uncertainties, its emphasis on critical data, adaptability, and quality improvement holds promise for enhancing the overall quality of clinical trials. It also has gained widespread

recognition for its potential to improve the efficiency and cost-effectiveness of clinical trials while maintaining the highest standards of quality and safety. As the landscape of clinical research continues to evolve, both approaches will play crucial roles, requiring careful consideration and adaptation to the specific needs of each study.

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## REFERENCES

1. Bhatt A. Evolution of clinical research: a history before and beyond james lind. Perspect Clin Res. 2010; 1(1): 6-10. PMID: 21829774; PMCID: PMC3149409.
2. Verma V, Mishra A, Gowrav G, & Nischitha N. Clinical trial monitoring: An overview of risk-based approach. *Journal of Young Pharmacists*. 2023; 15(2), 239–244. https://doi.org/10.5530/jyp.2023.15.33.
3. Asapu Yeshaswini, Thabitha Supriya Allada, C S Mujeebuddin. Monitoring in Clinical Trial. *Int. J. Pharm. Sci. Rev. Res*. 2020; 63(1): 32-39.
4. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). (2016). Good clinical practice. ICH E6(R2). available at: https://database-name.org/ich-guidelines/full-text/e6-r2.
5. CPGM 7348.810: Sponsors, Contract Research Organizations and Monitors (March 11, 2011), available at: http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133777.htm.
6. Expert T. Clinical trial monitoring: On-Site, remote & centralized monitoring. Credevo Articles. 2023, available at: https://credevo.com/articles/2021/10/25/clinical-trial-monitoring-on-site-remote-centralized-monitoring/
7. EMA Reflection paper on Risk-based Quality Management in Clinical Trials (18 November 2013), available at: www.ema.europa.eu/docs/en_GB/document_library/.../11/WC500155491.pdf.
8. Limaye N, & Jaguste V. Risk-Based Monitoring (RBM) implementation: challenges and potential solutions. Therapeutic Innovation & Regulatory Science. 2019; 53(2): 183–189. https://doi.org/10.1177/2168479018769284.
9. Williams G W. The other side of clinical trial monitoring; assuring data quality and procedural adherence. *Clinical Trials: Journal of the Society for Clinical Trials.* 2006: 3(6), 530–537. doi:10.1177/1740774506073104.
10. Ministry Of Health and Family Welfare Government of India. Good Clinical Practice Guidelines. 2015. Available at: https://rgcb.res.in/documents/Good-Clinical-Practice-Guideline.pdf.
11. Molloy S F, & Henley P. Monitoring clinical trials: a practical guide. Tropical Medicine & International Health. 2016; 21(12):1602–611. https://doi.org/10.1111/tmi.12781.
12. Jung S, Kang J W, & Kim T H. Monitoring in clinical trials of complementary and alternative medicine. Integrative Medicine Research. 2021; 10(2): 100666. https://doi.org/10.1016/j.imr.2020.100666.
13. Macefield R, Beswick A D, Blazeby J M, & Lane J A. A systematic review of on-site monitoring methods for healthcare randomised controlled trials. *Clinical Trials*. 2013: 10(1), 104–124. https://doi.org/10.1177/1740774512467405.
14. Agrafiotis DK, Lobanov VS, Farnum MA, Yang E, Ciervo J, Walega M, Baumgart A, Mackey A. Risk-based monitoring of clinical trials: An integrative approach. *Clin Ther*. 2018; 40(7):1204-12. doi: 10.1016/j.clinthera.2018.04.020, PMID 30100201.
15. Olsen R, Bihlet A, Kalakou F, Andersen J. The impact of clinical trial monitoring approaches on data integrity and cost—a review of current literature. *Eur J Clin Pharmacol.* 2016; 72: 399–412. https://doi.org/10.1007/s00228-015-2004-y.
16. Usher RW. PHRMA BioResearch Monitoring Committee Perspective on Acceptable Approaches for Clinical Trial Monitoring. *Drug Information Journal*. 2010; 44(4), 477–483. https://doi.org/10.1177/009286151004400412.
17. Hurley C, Shiely F, Power J, Clarke M, Eustace J A, Flanagan E, & Kearney P M. Risk based monitoring (RBM) tools for clinical trials: A systematic review. *Contemporary Clinical Trials.* 2016; *51: 15–27.* doi:10.1016/j.cct.2016.09.003.
18. Yamada O, Chiu S W, Takata M, Michiaki A, Shoji M, Kyotani E, Endo C, Shimada M, Tamura Y, & Yamaguchi T. Clinical trial monitoring effectiveness: Remote risk-based monitoring versus on-site monitoring with 100% source data verification. *Clinical Trials*. 2020; 18(2): 158–167. https://doi.org/10.1177/1740774520971254.
19. US Food and Drug Administration. Guidance for industry oversight of clinical investigations: a risk-based approach to monitoring. www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm269919.pdf. Accessed April 18, 2014.
20. Davis S, Pai S. Challenges, and opportunities for sponsors in conducting clinical trials during a pandemic. Perspect Clin Res 2020; 11:115-20.
21. Rosenberg M J. Key considerations in the transition to Risk-Based Monitoring. Therapeutic Innovation & Regulatory Science. 2014; 48(4): 428–435. https://doi.org/10.1177/2168479013519631.
22. A. Ghone, Applied Clinical Trials [Online] 01 October 2015. Available: http://www.appliedclinicaltrialsonline.com/centralized-monitoring-smart-reliable-approach.
23. Basics of Clinical Trial Centralised Monitoring [Online]. 11 January 2018, Available: https://www.appliedclinicaltrialsonline.com/view/basics-clinical-trial-centralized-monitoring.
24. Socra, & Socra. BULLSEYE: What is Targeted Monitoring All About? - SOCRA Blog. SOCRA Blog - Educational Content Supporting Clinical Research Excellence. 2019, August 1. Available: https://www.socra.org/blog/what-is-targeted-monitoring-all-about/

25. Klatte K, Pauli-Magnus C, Love S, Sydes M R, Benkert P, Bruni N, Ewald H, Arnaiz P, Bonde M, & Briel M. Monitoring strategies for clinical intervention studies. The Cochrane Library. 2021; 22(1):44-49. https://doi.org/10.1002/14651858.mr000051.pub2.

26. Singh N, Madkaikar NJ, Gokhale PM, Parmar DV. New drugs and clinical trials rules 2019: Changes in responsibilities of the ethics committee. Perspect Clin Res. 2020; 11(1): 37-43. doi: 10.4103/picr.PICR_208_19.

27. Vijayananthan A, & Nawawi O. The importance of Good Clinical Practice guidelines and its role in clinical trials. *Biomedical Imaging and Intervention Journal*. 2008; 4(1):18-24. https://doi.org/10.2349/biij.4.1.e5.

28. Vyas N. Future of risk-based monitoring in clinical trials. International Journal of Clinical Trials. 2020; 7(3): 221-228. https://doi.org/10.18203/2349-3259.ijct20203109.

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