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Reliability and feasibility of centralized monitoring approach in source data verification during clinical trials

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Abstract

As per ICH GCP, monitoring can be defined 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(s*)."* Clinical experiments are important for deeper understanding of how interventions work in humans. The aim of the monitoring of the clinical trial is to avoid errors that may compromise patient safety and results of the trial and enables more frequent monitoring of the integrity of the trial and could improve safety concerns by detecting errors earlier than expected. Risk-based monitoring in clinical trials is the process of identification, assessment, monitoring and mitigation of risks that could affect the quality or safety of a study. Centralized monitoring has a direct impact on the clinical trials. One of the most basic and fundamental need of centralized monitoring is to avoid the repetition in clinical trials, saving both time and Money. Central monitoring greatly influences the Patient safety, data integrity and monitoring costs in a clinical trial. This helps in increasing the effectiveness of the monitoring process reducing the burden on the sponsor. The basic and fundamental priority of a clinical trial is to ensure the safety and well-being of the subject. In this article, we will be focusing on how Centralized monitoring can increase the effectiveness and efficiency of the monitoring process and source data verification (SDV) in clinical trials with a special emphasis on Risk based monitoring (RBM).

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Introduction

Monitoring is considered as an important activity as it ensures quality in the clinical trial [1]. As per ICH GCP, monitoring can be defined 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(s)"* [2].

Clinical experiments are important for deeper understanding of how interventions work in humans. Monitoring of clinical trials is an essential drug development component with the aim of safeguarding subject safety, data quality and protocol compliance. Hence, it is essential that the clinical trials produce accurate, complete and relevant data. In order to achieve this, continuous monitoring is very essential [3]. Conventionally, in clinical trials the monitoring is conducted through on-site visits, where source data verification (SDV) is done. This method of on-site monitoring is cost consuming and accounts for a major budget of the clinical trial. Apart from being cost consuming, it is time consuming as well. This is where the significance of centralized monitoring (CM) comes into picture [4, 5].

Studies. CM The aim of the monitoring of the clinical trial is to avoid errors that may compromise patient safety and results of the enables more frequent monitoring of the integrity of the trial and could improve safety concerns by detecting errors earlier than expected [6]. CM is the most efficient way to ensure patient safety in the context of multicentre clinical research, as it enables the study team to identify malicious data trends on a proactive basis. CM Improves the quality of regulatory submissions with a direct impact on marketing approval time [7]. CM is a continuous process and it includes periodic assessments to account for potential latency in the identification and addresses issues that arise between these assessments and daily processes, as it uses thresholds to generate alerts and automated notifications, and to raise issues directly with the site monitoring staff [8].

In this article, we will be focusing on how Centralized monitoring can increase the effectiveness and efficiency of the monitoring process and SDV in clinical trials with a special emphasis on Risk based monitoring (RBM).

Risk Based Monitoring (RBM)

Risk-based monitoring in clinical trials is the process of identification, assessment, monitoring and mitigation of risks

That could affect the quality or safety of a study. The RBM method of monitoring the clinical trials, positively impacts various aspects like, subject selection, adherence and investigator involvement. The goal of RBM is to prevent important sources of error that threaten the quality of critical data. On RBM platform entire data is objectively evaluated in a standardized manner. RBM links the sponsor directly to the investigator, and reassures that the clinicians will act as a fair witness and report accurately to the sponsor [9].

The RBM plan specifies that 100% of the critical data be checked against the source records, and that 100% of the critical processes be validated to determine whether the established risks have been visually and logically examined as a result of the data management plan. It is a mixed strategy that involves on-site and central monitoring and focuses on the risks that could impact the collection of the most important data and processes required to achieve the goals of the research [10].

The RBM method uses initial risk assessment which is completed in the early stages of the trial and help in assessing the level of monitoring required. This helps in determining the number of visits by the monitor. High risk trials require more frequent visits when compared to low-risk trials [11]. Few of the RBM approaches include reducing the activities needed on-site, addressing data requests remotely through the interrogation of electronic systems, obtaining consent from participants to enable documents like consent form to be submitted to the Central Evaluation Coordinating Center [12].

The method of RBM is an effective method for monitoring and ensuring human subject protection and ensures the reliability of the results obtained in the trial. It also detects critical data and process errors saving travelling time and costs for on-site monitoring.

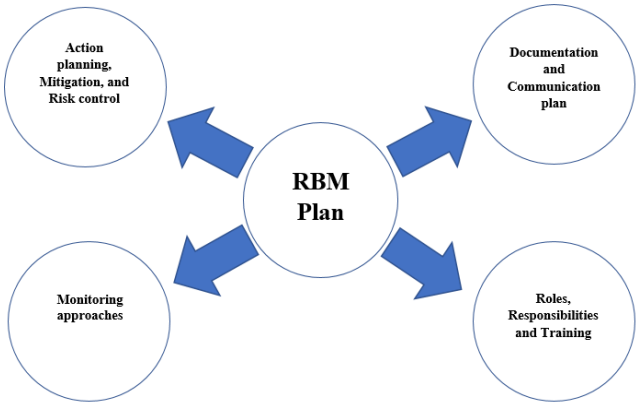

Figure 1. The Risk Based Monitoring Plan

Source Data Verification (SDV)

For monitoring of clinical trials the FDA issued a guide line stating 'The most effective way to assure the accuracy of the data submitted to the FDA is to review individual subject records and other supporting documents and compare those records with the reports prepared by the investigator for submission to the sponsor'. SDV is a verification for the conformity of data which is provided in the case report forms with the source data and it ensures that data collected is reliable and enables the reconstruction and evaluation of trial and thus fulfilling the ICH E6's requirement of accuracy, completeness and verifiability with the source documents [13].

These guidelines which were issued in 1988 have led to a consensus within the industry that the SDV of 100% of all the entered data was necessary to comply with the requirements of FDA for data quality and integrity [14].

The on-site monitoring consumes a sum of clinical trial costs. The resources which are dedicated to SDV have a very minimal impact on the conclusions of the study. While SDV can be considered as an effective way to detect the errors such as transcription errors, human errors etc., it is not very efficient when it comes to missing information or data which the staff considered of no importance or fraud. These problems arise during manual on-site monitoring and can be overcome by Central monitoring [15].

Various Approaches of SDV

Standard SDV Approach

It assumes that the source data is verified with the source documents and records. The problem with this approach is that the implementation is very expensive and time consuming.

Random SDV Approach

In this method SDV starts at a low level where very few data points are selected for SDV. Based on the quality of results produced the SDV level is increased.

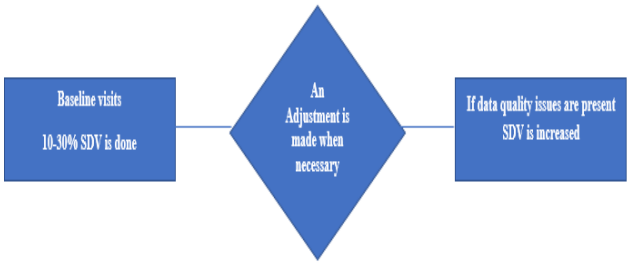

Figure 2. Random SDV Approach

Declining SDV Approach

It is the reverse of Random SDV approach. It initially begins with 100% SDV and is slowly reduced. It is an improved version of Random SDV and helps in detection of errors early in the trial.

Figure 3. Declining SDV Approach.

Three-Tired SDV Approach

In the Three-Tired SDV approach, a study team including a statistician determines a list of variables that should be included in the 3 tiers. In Tier 1, 100% SDV is done and variables like AEs, dates, dosing and key variables of analysis are included. Tier 2 involves 10-20% SDV, and variables like vital signs and labs are included. Tier 3 involves 0% SDV and includes variables like physical examinations.

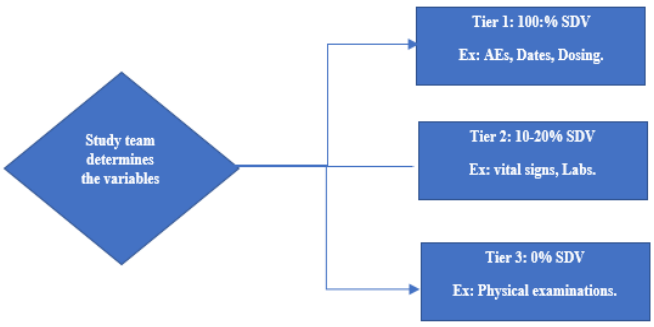

Figure 4. Three-Tired Approach

The impact of centralized monitoring on clinical trials

Centralized monitoring has a direct impact on the clinical trials. One of the most basic and fundamental need of centralized monitoring is to avoid the repetition in clinical trials, saving both time and money. Data quality and Patient safety are the essential objectives of Centralized monitoring. Several sponsors are turning their thoughts towards centralized monitoring as it helps ensure the dispensing of resources mindfully, without compromising with the clinical quality. Keeping time constraints and limited assets in mind, the method of centralized monitoring considers the priority to be on the main aspects and the most important data. This technique has a very complex approach which helps in characterizing the risk evaluation from very beginning and staying with it till the end of the study. [16]

Role of Central Monitoring In Increasing the Effectiveness of the Monitoring Process

Central monitoring greatly influences the Patient safety, data integrity and monitoring costs in a clinical trial. This helps in increasing the effectiveness of the monitoring process reducing the burden on the sponsor. In the crucial zone of money and time, RBM helps in reviewing all the information obtained and thereby assessing when the best income would arise. With the site visits decreased, more emphasis and attention can be given to individual patients and more detailed data collection is possible. It can also offer a clearer vision for master plan of the study and provide a key context for the process [17].

Subject Safety

The basic and fundamental priority of a clinical trial is to ensure the safety and well-being of the subject. Centralized monitoring involves various methods like RBM and Central Statistical Monitoring (CSM), which ensure prompt and continuous adverse event reporting by reviewing data on subject safety and eligibility in real time. CSM helps in efficiently identifying the centres that recruit ineligible patients and centres who have higher adverse event rates than the average [4, 18].

Data Integrity

Data integrity and collection of high-quality data is a crucial aspect of clinical trials, as it decides the validity of the trial. Performing 100% SDV only offers a marginal error rate Reduction and it is a myth that it provides error-free data. Various studies have been performed to assess the impact that 100% SDV and central monitoring have on the Integrity of data. Andersen et al. have published a study on empirical post hoc analysis of a three-phase III RCTs, where they compared the impact on data quality by using 100% SDV with partial SDV. The results suggested that 100% SDV offers a very marginal reduction in the errors [13.] Tudur smith et al. also performed a similar study with 533 randomized subjects across 75 sites. The study found no systematic patterns that SDV would impact the primary outcome of trial [19]. Mitchel et al., performed a study where they compared 5581 source documents in 29 CRFs to assess the efficiency of SDV. 13 of 29 unique forms underwent unspecified changes as a result of source data verification with 48 changes. Surprisingly, these changes represented an error rate of 0.86, and 66.6%. Currently there is a limited evidence to support that 100% SDV can impact the outcome of the clinical trial, but, we can say that central monitoring has an advantage over on-site monitoring when it comes to fraud, apparatus errors due to calibration, biased scores, and detecting trends in data propagation [21].

Monitoring Costs

As we have seen in earlier sections that centralized monitoring helps reduce the monitoring costs to a great extent, it also contributes in increasing the profits to the sponsor. Nielsen et al. explored the risks and benefits that were associated with the decreasing SDV in 4 different approaches of SDV namely, Random, Declining, Three-tired and Mixed approach. Basing on this study authors concluded that the mixed approach was found to be more cost efficient and optimal among all [22]. Eisenstein et al. used economic model to show that total trial costs can be reduced by 21.1 % by decreasing the intensity of on-site monitoring.

Citing the above studies, we can conclude that central monitoring is a more feasible way and reduced the query rate. Various costs of reiteration, travel and repeated verification can be minimized by following the method of centralized monitoring [23].

Discussion

Average number of medicinal products per billion dollars of development costs have reduced by a great margin since 1950. This calls for identification of various methods which will reduce the cost of drug development [24]. This review summarizes various approaches of SDV and how centralized monitoring could reduce the costs of drug development. The Main aim was to show how we could balance the cost reductions and yet maintain the quality of data without affecting the validity of the clinical trial and ensuring the well-being of trial subjects [24]. The association between

subject safety, data quality and the extent of monitoring cannot be explained clearly [4]. but it would be reasonable to assume that performing SDV on the on-site subject records has a positive impact on safety outcomes. Targeted SDV is very valuable and important when it comes to non-reported adverse events and serious adverse events. It is very important in documenting the safety of the investigational medicinal product.

Based on the results from above works, we can conclude that the monitoring costs can be significantly reduced by SDV by using remote/ central monitoring. Central monitoring is a very reasonable alternative to on-site monitoring method for source data verification as the data can be assessed by electronic means and remotely [25].

By setting up an effective system of remote monitoring its benefit can be taken without spending additional time on monitoring data which is not critical and without compromising with the data integrity and safety of the trial subjects. But this has only been proven in trials which involved very fewer trial subjects and this might not be the case in trial involving larger trial subjects.

Based on reviewing the literature, it wouldn't be wrong to conclude that the concept of error-free data in not a realistic one. But, the main reason why these errors occur is due to transcription between source data and Electronic Data Capture (EDC) systems. This could be concluded from studies by Mitchel et al [5].

Conclusion

Based on the literature referred, we can conclude that On-site monitoring of SDV is not a rational method of ensuring data integrity and safety of subjects, due to high costs and time taken. Centralized monitoring is an alternative method to on-site monitoring which can help in better data accuracy balanced with time and cost. Reduced on-site monitoring along with Centralized and Risk based monitoring would be a model solution to reduce monitoring costs, improving data quality and accuracy reducing the burden on the sponsor.

Conflict of interest

The authors declare no conflict of interest.

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