

Review Article

Critical utility of e-solutions in risk based monitoring

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ABSTRACT

As the clinical trial industry is evolving from a traditional 100% SDV (source data verification) approach to reduced SDV & Centralized Monitoring by applying a risk based monitoring (RBM) approach, hence forth leveraging of e-Solutions and real time data integrations would be critical in RBM. Technological considerations are critical to collect data real time to assess, monitor and mitigate risk in compliance with Good Clinical Practices. This article will examine the importance of e-Solutions and real time analytics in alignment with various systems for developing an effective RBM strategy.

Keywords: Source data verification, Risk based monitoring, Good clinical practices

INTRODUCTION

Risk based monitoring (RBM) aims to reduce the number of on-site monitoring visits, and is a paradigm shift from a traditional monitoring approach i.e. 100% SDV to be done at the site. Key regulatory bodies such as the FDA, the EMA and other consortiums such as TransCelerate BioPharma have endorsed this approach.

Unlike what is the wider industry perspective that the regulators mandate 100% site monitoring, the FDA, in its guidance for the industry 'Oversight of Clinical Investigations - a Risk-based Approach to Monitoring (August 2013)', has stated that: "No single approach to monitoring is appropriate or necessary for every clinical trial. FDA recommends that each sponsor design a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. Ordinarily, such a risk-based plan would include a mix of centralized and on-site monitoring practices."¹⁻⁵

Thus, RBM, which involves centralized/offsite monitoring, is an evaluation carried out by sponsor personnel or representatives (e.g., central monitors, data management associates, or statisticians) at an offsite

location i.e. not at the sites at which the clinical investigation is being conducted, based on risk assessment for the study & site, and accordingly directs the requirement for centralized/remote monitoring, or on-site monitoring.⁶

IMPORTANT TASKS THAT NEED TO BE PERFORMED IN RBM

As identified by the FDA, TransCelerate BioPharma, and other experts, some common principles are:

1. Risk assessment: The important point to note is that RBM is a methodology and not a standard, there are no set of standards existing today for RBM for example, the exact standard to calculate risk. Hence industry players are defining their own standards to achieve common goals, which would comply with regulatory requirements.

For e.g., the potential program level risk, study level risk or site level risk may be pre-defined, and calculated before study initiation, or may be determined after a fixed number of patients are 100% SDVd to assesses that the risk category or score under which the study falls, based on which it would be decided whether the reduced

SDV/SDR model is applicable or not. The risk score will also be helpful in defining the percentage of SDV/SDR that needs to be performed.

2. Implementation of Key Risk Indicators/Monitoring Triggers based on the cadence (categories) and their thresholds to mitigate study risk
3. Applying centralized/remote monitoring
4. Reduced SDV/SDR, 0% SDV with an SDR Model etc.
5. Centralized review of critical data.³

On-site review is time consuming, expensive, prone to error, and limited in its ability to provide insights for data trends. In contrast, risk-based monitoring (RBM) makes use of a centralized review of clinical trial data and study & site metrics to determine what, if and when clinical sites should receive more extensive quality review or intervention.⁷

E-SOLUTIONS AND RBM

e-Solutions e.g. EDC, IWRS, E-Diaries etc. are key factors to make RBM successful. Utilizing e-Solutions is of utmost importance in RBM. Some of the advantages are as follows:

Real time data tracking

In the centralized and reduced SDV/SDR model, e-Solutions will enable real time evaluation of data and the implementation of the risk mitigation strategy for RBM. For example:

Potential IP dosing non-compliance

On-time action for subjects through centralized review, which is not possible using paper diaries, because in paper diaries data is either be reviewed by site staff retrospectively, when the subject appears for his next visit and or by the site monitor on his next monitoring visit, as a result of which real time action is not possible.

Delayed data entry

Immediate action for missing pages in the EDC system for subjects through centralized review, without performing interim on-site visits is not possible using paper CRFs. Tracking the real time EDC data entry status for the study and site helps one to plan the appropriate risk mitigation strategy. In the case of paper CRFs, it is a challenging task because it requires an on-site visit to confirm whether all the pages are up-to date and centralized review is possible only once the CRFs from the site are retrieved, resulting in a significant time lag.

SDV backlog

Immediate action for outstanding SDV pages in the EDC system for subjects through centralized review without performing an interim on-site visit, which is not possible using paper CRFs. Not only will tracking the real time EDC entry status for the study and the site help outline the risk mitigation strategy, it will also save time and money otherwise spent on performing an on-site monitoring visit.

Query resolution

Query resolution is time consuming while using paper solutions as compare to e-Solutions, and there is a risk if pending unresolved queries go beyond a certain threshold decided for the study. e-Solutions will help detect unresolved queries on-time and the required action can be taken immediately.

Potential fraud and misconduct

e-Solutions can help raise auto triggers on a real time basis as soon as data is entered in the system and accordingly inspections / investigations to assess potential fraud and misconducts can be planned. e-Solutions will enable immediate access to data and help generate real-time reports

Real time data analysis

In the centralized/RBM model, real time data is important to analyze data at a set frequency; it will help to plan for timely risk mitigation. For example:

IWRS/IVRS

They will help to track site-wise and study-wise on-time screening, enrollment, screen failure, discontinuation status of the subjects which will help to analyze real time data and perform risk mitigation in a timely manner to address issues such as a very high screen failure rate at a site or in a study.

Data integration & analysis

By integrating e-Solutions, for example, integrating EDC, e-diaries, IWRS, labs. CTMS, other portals etc. and analyzing the data in a holistic manner, one can establish data trending and look for outliers – thus helping outline RBM.

DATA TRANSFER ERRORS

e-Clinical solutions can put an end to data entry errors which may result when transcribing data from paper into a database and, also decrease manual intervention. It will increase data accuracy (wherein data is directly pulled from source such as EMRs, labs, devices, etc.). Accurate data is so essential when a RBM approach is used as

actions are based entirely on triggers flagged by data for various Key Risk Indicators for a study.

TRACEABILITY

In order to be 21 CFR Part 11 compliant, in audit trials all the data changes must be tracked within the EDC systems. Also, risk management/business continuity plan must be planned by Vendor. Because, it is possible to track any changes in the EDC systems henceforth it is easier to answer FDA reviewer's question.^{4,6}

PATIENT SAFETY

Utilizing EDC systems and applying quality by design model helps to lead improvement in data quality, and more effective issue management. Bringing integrated quality risk management approach of RBM while utilizing EDC system helps for faster resolution of query back log, data cleaning timelines and thereby reduction in a study time. Also, faster notification of AEs as compared to paper based studies can help for more effective safety management. Leveraging-solutions in tandem with RBM can play significant role in this.^{4,6}

MONITORING MORE STREAMLINED

E.g. with the use of e-Solutions RBM can lowers the cost of monitoring visits. In addition e-Solutions is helpful for early identification of data discrepancies, protocol deviations, potential frauds and misconduct etc. henceforth reducing the time spent by site monitors at sites.

LIMITS AND CHALLENGES OF E-SOLUTIONS

Although, there are number of benefits of EDC, however it is not adopted completely in all the segments of clinical research. The reason of low adoption may be due to the high cost involved of proprietary EDC systems along with their implementation cost.

It is a usual understanding that paper-based studies are faster and involves lesser cost to implement compared to EDC studies. It is evident that paper based studies can be started faster; as per the data available shows that their overall duration is as much as 30% longer on average.

Technological advancements have helped to reduce the study-build time. Study form reusability has made it possible to deploy complete EDC study in much less time compared to earlier.

Also, one of the major discouragements in adoption of EDC is the initial cost involved, predominantly for preclinical or phase I trials with lower budgets. The most notable costs involved are for employing vendor(s) & other resources e.g. Clinical data management experts, programming experts etc. And also setting up the system cost is involved including hardware and software cost.

Once the initial setup is done, subsequent study costs on an ongoing basis for each new clinical trial can become marginal.^{4,6}

CONCLUSION

One interesting finding from the TransCelerate BioPharma consortium (a non-profit organization focused on advancing innovation in research and development) was that SDV may be less critical to lowering risk than commonly thought. Member companies conducted a retrospective analysis to assess queries identified via

SDV to find the percentage of SDV-generated queries in critical data. The total was only 2.4%, suggesting that SDV has little impact on the quality of the data.

Hence, this risk-based approach to monitoring implies more focused vigilance to improve data quality, and integrity. New and emerging technologies play an important role, and hence e-Solutions enabled RBM helps in early identification of discrepancies, data entry errors, protocol deviations, potential frauds and misconducts etc. thereby reducing time spent by monitors at sites.^{2,3,4,6}

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