

## Editorial

# Impacts and Implications of Risk Based Monitoring: A Contract Research Organization (CRO) Perspective

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## Abstract

During the past decades, the complexity of clinical trials have grown dramatically due to geographic dispersion, site related issues, treatment choices, standard of care and regulatory uncertainty. The uncertainty has created opportunity for the Risk Based Monitoring (RBM). RBM has emerged as the future of clinical development. This approach is supported by the US-FDA, European Medicines Agency (EMA) and several other regulatory agencies. Efficient planning lays the foundation of an effective risk-based monitoring strategy. Fabrication of data, fraud, data distribution errors and other data anomalies that can be readily found by risk based monitoring policies and procedures. RBM improves quality and efficiency of sponsor to oversight clinical sites and help to save significant cost. It helps to quickly identify signals that could affect quality and operational performance. Risk based monitoring has matured but is still gaining in efficiencies.

**Keywords:** Biotech; Clinical Trials; CROs; Impact and Implications; Pharmaceuticals; Risk Based Monitoring

## Introduction

The future of clinical trial monitoring is at a crossroads. Traditional monitoring is still dominates the market but risk based monitoring has emerged as the effective tools to manage global clinical trials without compromising ethics, patient safety, quality and regulatory framework. RBM facilitate more efficient clinical trial conduct with enhance focus on quality and ethics related to patient safety. Early risk identification will help to plan mitigation strategy with continuous risk monitoring throughout Clinical development [1]. The FDA cites the most commonplace compliance deficiencies as inadequate oversight by the Investigators, consenting issues, poor data management and record keeping, protocol deviations, IP/RLD accountability issues, Randomization errors and subject protection issues. To address these deficiencies, Risk-Based Monitoring (RBM) has emerged as a powerful, technology-based approach.

## Monitoring in Clinical Trials [2]

Monitoring refers to oversee the conduct of, and reporting of data from, clinical investigations, including supervision of study site staff and third-party contractors. Clinical site monitoring accounts around 30-35 % of total cost Monitoring has been considered as one of the secured measure to ensure data integrity. Key job in monitoring is to do source data verification, site process and procedures, communication with site team members and ensure accuracy of data submitted to the regulatory authorities. It is quality control tools for the sponsor to judge whether the activities are being carried out as per approved protocols/ SOPs and regulatory norms or not. FDA recommends a quality risk management approach to clinical trials.

## Current Monitoring Practices [2,3]

A range of different practices has been used to monitor the conduct of clinical trials across globe. These practices differ in intensity, methodology, focus and centralized monitoring activity.

- Monitoring to high risk sites based on central monitoring findings i.e Targeted monitoring visit.
- Onsite visit (By Clinical Research Associates (CRA) or sponsor representatives) as per defined monitoring plan/ or developed as per protocol visits. For major efficacy trials, Onsite monitoring visit is preferred practice followed by most of the companies. Typically, CRAs visit site at approx. 4 to 6 weeks intervals to perform 100% source data verification. It's one of preferred way to meet sponsor obligations set by FDA.
- Improves the efficiency of Clinical Research Associates (CRAs), as they concentrate on the sites that need help and allow competent sites to precede without unnecessary interference.
- Dramatically improves the reliability and verifiability of study data, avoiding unpleasant surprises upon regulators' review.
- It has the potential to reduce overall monitoring costs in most studies.
- Centralize data checks helps to prioritizing site visits and improve the effectiveness.

### **Risk Based Monitoring [1-4]**

Definition: It is "Strategic" monitoring based on technologically-enabled, risk-based algorithms that focus monitoring resources on the locations and activities where they are most needed. In 2011 the U.S. Food and Drug Administration, the European Medicines Agency and the United Kingdom's Medicines and Healthcare Products Regulatory Agency issued papers intended to "Open up the discussion on approaches to clinical trials and to new thinking, in order to facilitate the development of proportionate clinical trial processes". In August 2013, the FDA issued draft guidance for "A Risk-based approach to monitoring" with below objective "The overarching goal of this guidance is to enhance human subject protection and the quality of clinical trial data by focusing sponsor oversight on the most important aspects of study conduct and reporting. Below are the key steps while performing RBM

1. Identification of key processes and critical data points: It is important to know which data elements are vital from safety and efficacy point including eligibility criteria.
2. Risk assessment -Cause and impact analysis.
3. Development of Risk Monitoring Plan (RBM) - FDA encourage developing robust monitoring plan at the start of clinical trial to address data quality challenges. Here, the approach is to develop more focus and vigilant plan to mitigate likely risks to the data quality and monitor processes that linked to human subjects and ethics by protecting data integrity. It is important to ensure highest level of communication to all the parties involved in risk based monitoring.

The basic concept of RBM is to focus attention on the data, documents, and processes, which are critical and important. There are several advantages of Risk based monitoring:

- RBM helps in early identification of problems so that they can be remedied quickly, protecting patients and preserving the overall integrity of the study.
- Holistically identifies risk of failure
- Delivers fit for purpose quality -flexible to study and regulatory need.

### **Impact and Implications of Risk Based Monitoring**

Use of modern data technologies for remote risk-based monitoring can help reduce non-value-added rework, people and paper in clinical trials and help speed up time to statistical report. The RBM metrics may be considered in to total 4 categories:

1. Safety - Identify key trends in vitals and AE/SAEs reported during conduct of study.
2. Efficacy - Identify trends and monitor primary and second end points data points.
3. Ethics - Monitor key regulatory and ethical issues
4. Data quality risk-Monitor long data entry cycle times, patient visits.

Use of Computer algorithms is useful to identify number of slow moving events which is hard to catch in regular 4-6 weeks study monitoring visit.

### **Challenges in Risk Based Monitoring (RBM) - A CRO perspective [1-8]**

Industry is still in the transition phase and perplex towards the adoption of Risk Based Monitoring as the process is still evolving. Below are the key implementation challenges:

- Failure in the planning and execution of any activity during risk based monitoring may raise the concern over entire clinical trial data generated during the study.
- Maintaining quality standard across various therapeutic areas is difficult for most of CROs.
- It is difficult to implement recommended regulatory changes in Risk based monitoring process and procedures in defined time period.
- Lack of internal knowledge, system, and procedure is one of key hurdles during implementation of RBM.
- Top management support to replace traditional monitoring system considering risk/ rewards.

- Implementation cost
- Ensuring patient safety, data integrity & regulatory compliance throughout clinical development
- Variable needs and monitoring priorities from different sponsors
- Expectation-setting with sites.
- Managing monitor support expectations
- Perform change and resource management based on RBM plan.

## Conclusion

In spite of support from various regulatory agencies like FDA, EMEA, implementation of Risk Based Monitoring is still less across industry. The RBM policies and procedures bring as much as 20-30% cost reduction over traditional trial execution approaches with greater efficiency and more predictable outcome at much lower costs. By focusing on key data points and sites requires highest scrutiny help for efficient management of clinical trial. It is important to create various trigger/alert (e.g. Lab parameters, study Arm, safety signals, study drug administration, visit schedule) based on protocol design at the start of study to identify risk throughout execution period. It is concluded that, efficient planning lays the foundation of an effective risk-based monitoring strategy.

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