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WHITE PAPER

# Centralized Monitoring in Early Phase Clinical Trials

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# Introduction:

Early phase clinical trials demand increased vigilance to ensure participant safety and the veracity of trial data. Historically, the industry considered frequent onsite monitoring by a sponsor representative to be the most effective way to ensure this. With the increase of data acquisition tools, better utilization of available data, and in-depth research into the efficacy of monitoring methods we now understand that a harmonized central monitoring strategy, in combination with traditional onsite monitoring methods, is optimal to ensure quality in early phase clinical trials[5, 6, 7, 12, 13, 14].

Quality is the foundation of clinical trials. Without quality, it is not possible to produce trustworthy data to ensure the protection of trial participants. Quality is defined as the absence of meaningful errors1 that impact critical trial processes or data. These are the Critical to Quality (CtQ) factors that affect participant rights, safety, wellbeing, data integrity, and the very information required to answer the question the protocol poses[2].

Inadequate quality in clinical trials may endanger the safety, rights, and wellbeing of trial participants leading to site closure, patient harm, or study termination. Poor quality data may not be deemed accurate and reliable and unable to support a clinical study report conclusion, which may mean the participants were exposed to the additional risk of an interventional trial unethically and that extensive time and resources were ultimately wasted.

Conducting quality clinical trials ensures the protection of clinical trial participants, data integrity, and improves lives by providing access to life-changing treatments[2]. Additionally, quality clinical trials require significantly less time to achieve database lock[3], effectively reducing the burden on resources and budgets.

# Monitoring

Monitoring, typically by a Clinical Research Associate (CRA) and performed at the clinical trial site, is one of the core activities to ensure quality in clinical trials[4]. The objective of monitoring is to protect participant rights, safety, and well-being, and to ensure data integrity[4]. Historically, onsite monitoring has focused on source data verification (SDV) as the primary measurable metric intended to increase quality. Source data verification involves the CRA comparing source data against trial data and verifying its accuracy and compliance with the principles of ALCOA[4]. The 1988 FDA Guideline, 'Monitoring of Clinical Investigations' set the expected standard of 100% SDV to ensure quality[11]. After all – surely with increased review of trial data you would expect a proportionate yield in quality, right?

However, a complete 100% monitoring strategy is now considered an ineffective and inefficient means to ensure quality of trial data[13]. Not only that, but so much focus by the CRA on the Source Data Verification (SDV) of every single data point detracts from other critical monitoring tasks such as Source Data Review, IMP accountability, and reconciliation of study document to name a few. Furthermore, this singular task limits the potential to compare the data between participants and sites.

When reviewed as a monitoring process, full SDV offered no statistical advantage to partial SDV, and SDV alone could not achieve a 0% error rate[5]. Current findings show that SDV only impacts 1% of the eCRF data on average, but accounts for approximately 15% of the total cost of research[6].

The solution to increasing quality in monitoring is to supplement targeted onsite monitoring with central monitoring[7].

**"Centralised monitoring is the risk-based, remote evaluation of aggregate data against predetermined thresholds for quality and identifies potential issues with data veracity and data reporting."**

ICH GCP E6 (R3) requires the identification of missing data, inconsistent data, data outliers, unexpected lack of variability, data trends, such as the range, consistency and variability of data within and across sites, potential data manipulation, and data integrity problems; all of which can be difficult to identify by onsite monitoring alone[4]. Central monitoring methods are fundamental for compliance with ICH GCP E6 (R3) and to increase trial oversight and quality.

## Same objects, different methods

Participant rights, safety and well-being Data integrity Compilance
with protocol, ICH, GCP, and regulations

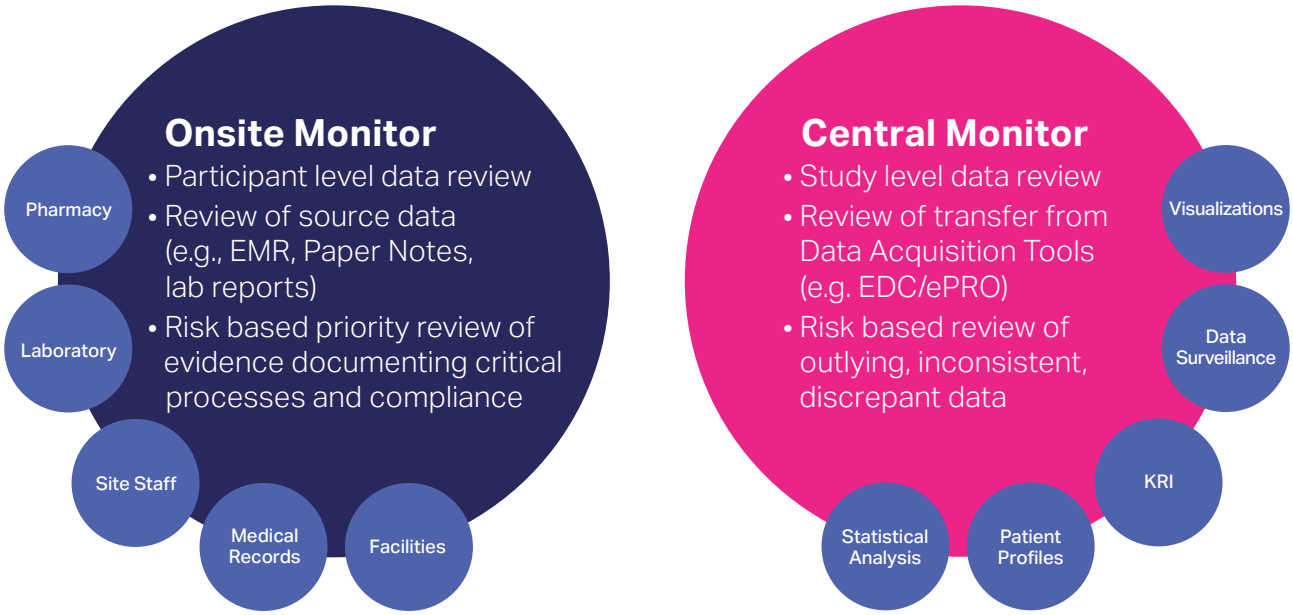


*Figure 1: A comparison of monitoring methods*

# Comparing Monitoring Methods

Implementing central monitoring in early phase clinical trials significantly improves quality, increasing participant safety and data integrity, reducing the time and cost to achieve database lock and marketing approval.

Drug developers can utilize three component methods for monitoring to ensure quality: onsite, remote, and central. To determine the optimal method to use for various aspects of a trial, it is important to understand the effectiveness of each type and its limitations.

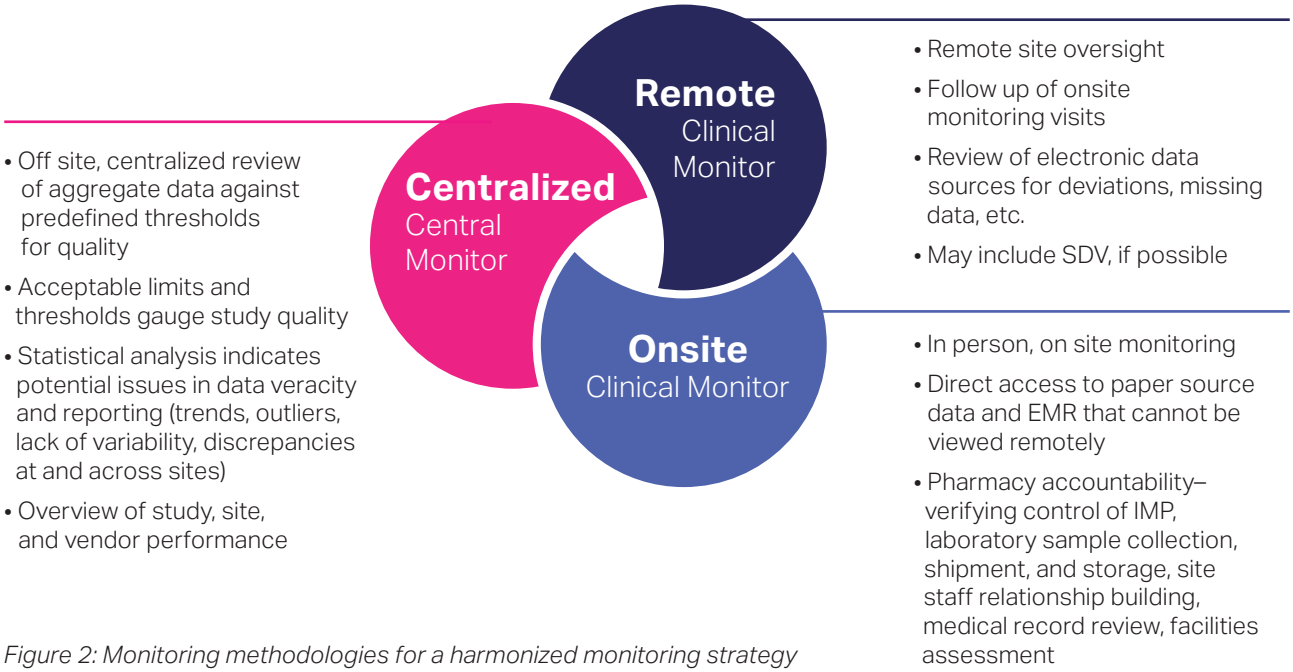


*Figure 2: Monitoring methodologies for a harmonized monitoring strategy*

# Early Phase Monitoring

Early phase trials typically focus on safety and tolerability, dose finding, pharmacokinetics, and pharmacodynamics (PK and PD), and have fewer participants, increased invasiveness, and quantity of assessments, and are often more complex than later phase trials[8]. The smaller participant sample size may, at first glance, lead to the postulation that central monitoring techniques may not be as effective in early phase monitoring, as many central methods require a minimum threshold of data to perform powerful enough, statistically significant comparative analysis. However, central monitoring is a broad term for a wide variety of monitoring activities that increase quality and enhance the efficacy of onsite monitoring[12]. In addition to the review of acceptable ranges, such as study level quality thresholds set as QTLs or KRIs, central monitoring might include an exploratory review of data to confirm correct IMP dosing, dose modifications, dose withdrawals, eligibility, unreported safety events, protocol deviations, visit windows, and much more. The divide-and-conquer approach enables the additional vigilance early phase trials require. This consists of the CRA reviewing records on-site – data point by data point. At the same time, the central monitor is targeting the data as aggregate and performing comparative analysis of reporting rates, and identification of high-risk sites and participants. Additionally, the finding of central monitoring may be of particular support to medical monitoring as both the results of central monitoring and the use of a central monitoring platform make medical review more efficient and effective.

# Benefits of Central Monitoring

Key benefits of central monitoring in early phase trials include increased vigilance of participants' safety and data in the review of eligibility, consent, protocol compliance, recruitment and retention, site and vendor performance, and the identification of discrepant data, patterns, outliers, and trends.

The identification of CtQ factors along with risk assessments for studies and sites enable project teams to determine participant quality measures for quality thresholds. Regular monitoring of these thresholds enables identification of risk signals so that teams can proactively mitigate risk ensuring the timely resolution of issues.

Early phase and site performance risk factors drive the customized and targeted central monitoring review considerations. Central monitors work directly with the clinical monitoring team communicating findings and receiving qualitative site performance summaries that drive targeted monitoring focus and follow up. Root cause analysis of findings actively prompts the adaptation of monitoring strategy to effectively prevent the recurrence of noncompliance.

Central monitoring systems allow for real-time visualization and assessment of trial data from multiple sources. This enables identification of inconsistent, outlying, and unexpected data, lack of data variability, data trends, such as the range, consistency, and variability of data within and across sites, potential data manipulation, data integrity problems, and device errors due to calibration. Trend analysis and escalation proactively reveal and resolve potential areas affecting quality.

Effective monitoring strategies are not just restricted to the onsite and central monitoring team but also include collaboration with medical monitoring and data management. Open communication and knowledge sharing facilitates a holistic method of ensuring participant safety and data integrity, reduces silos, increases the speed of data cleaning, and enables optimal conditions for expeditious database lock.

# Critical to Quality

Crucial to performing effective central monitoring is identifying what is meaningful to ensure quality within the clinical trial. Project teams identify CtQ factors and perform the initial risk assessment to set quality thresholds. These thresholds may be in the form of Key Risk Indicators (KRIs), Quality Tolerance Limits (QTLs), or acceptable ranges, and measure study, site, and participant quality. Thresholds are quantifiable metrics based on CtQ that can be measured and observed to signal that quality is in or out of range.

# Acceptable Ranges in Early Phase

Early phase studies tend to have endpoints relating to safety and tolerability. The type of thresholds that would be most effective for early phase studies would track rates of SAEs and AEs, compliance of safety procedures, and timeliness of safety reporting. The most optimal thresholds are actionable and provide predictive trends, meaning that they anticipate potential safety risks ahead of impact.

*Table 1: Potential Early Phase Trial KRIs*

| KRI | Function | Threshold comment and Potential Action Trigger |
|---|---|---|
| Rate of Serious Adverse Events per participant month | Early identification of serious safety trends/incidences | Customized to the expected rate – trigger medical monitoring review and onsite monitoring |
| Rate of Adverse Events per participant month | Early identification of safety and tolerability trends, protocol related/trial design issues | Customized to the expected rate – trigger site contact and safety review |
| Safety procedure compliance (missing assessments – vital signs/ECG/physical exam etc.) | Oversight of protocol compliance, meeting endpoints, and safety concerns | Lower threshold - trigger site contact and root cause analysis, Upper threshold - trigger site recruitment hold |
| Time between Adverse Event occurrence and reporting | Confidence in missing safety reporting, site performance trend | Customized to data entry expectations – trigger site contact, training, Root cause Analysis |
| Withdrawal rate (related to Adverse Event) | Oversight of tolerability and retention | Customized to the expected rate – trigger site contact, activation of backup sites |
| Lab abnormality rate (clinical significance) | Identify emerging safety signals | Customized to the expected rate – trigger medical review |

In addition to customized thresholds, general areas of threshold review reveal quality trends and risk indicators in performance metrics such as data cleaning and compliance.

*Table 2: General Quality Thresholds*

| | |
|---|---|
| Manual Query Rate | Data collection and data cleaning, site performance |
| Non-System Query Delay | |
| System Query Delay | |
| System Query Rate | |
| Percent Missing Visit | |
| Percent Out of Window Visit | |
| Protocol Deviation Rate | |

Regular monitoring of these thresholds allows for proactive identification of risk signals that project teams can mitigate, ensuring timely intervention and resolution of potential issues. When study teams review regularly and centrally, they proactively identify issues long before database lock allowing time for corrective action.

# Central Monitoring for Improved Quality

Central monitoring review utilizes the analysis of aggregate data with thresholds and statistics to effectively identify potential quality issues. A well-designed central monitoring platform enables the central monitoring manager to identify inconsistent, outlying, and unexpected data, unexpected lack of data variability, data trends, potential data manipulation and data integrity problems and much more! Utilizing the latest tools and technology helps to enhance overall quality. For example, Medidata Clinical Data Studio as it is an efficient and effective system agnostic platform that employs Machine Learning (ML), Artificial Intelligence (AI), and sophisticated algorithms to make the identification of quality concerns and set up of acceptable ranges as easy as possible.

The ability to compare all generated data to identify potential anomalies in reporting is incredibly powerful in ensuring the quality and veracity of trial data. Some common areas/anomalies that are more easily found in consolidated data include:

- visits are happening on weekends or holidays
- potential duplicate participants
- sites are rounding data to the nearest 0 or 5
- entering the same values across multiple visits or participants
- event incidence
- over or under reporting of AEs
- concomitant medications
- medical history at a glance

Ongoing central review of data has been shown to prospectively identify and enable resolution of the type of issues that have caused delays to data lock and caused rework in studies that do not use central monitoring review.

**The result of central monitoring is that studies are completed sooner, with less time, costs, and resources wasted on issue resolution and out-of-scope activity, and data is of higher quality[12, 13, 14].**

# Early Phase Risk Factors

Although an effective central monitoring strategy is highly customized to the specific risk factors that affect the trial, there are some risk factors that occur more often with larger impact in early phase trials. Aspects that explicitly increase the safety risk of early phase trials are if the trial is First-in-Human or a dose finding or combination trial, if it involves vaccines or biologics, if the trial is being conducted in a low-income nation, or if the participants have a low BMI[9]. An awareness of these increased safety risks, and the other trial specific risks identified in the initial risk assessment meeting enable the team to develop comprehensive risk mitigation strategies to embed directly into the monitoring plan for both onsite and central monitoring. Each critical process and critical data point would have a corresponding monitoring method or combination – onsite, remote, or central – designed to provide oversight and verification of safety, data integrity, and compliance.

# Early Phase Monitoring Strategy

An optimal early phase monitoring strategy will utilize each of the three prongs of monitoring methods to ensure participant safety and data integrity. Both the onsite monitors and the central monitors have the same objective but approach the task differently. Central and onsite monitoring must be part of a unified strategy where communication and collaboration is encouraged so that qualitative site and participant performance summaries are shared. The qualitative results form part of the central monitoring analysis that supports the proactive targeting of monitoring resource where and when it is needed.

Onsite monitoring is critical for early phase clinical trials in non-healthy volunteers due to the increased safety risk to the participant. Due to the proven lack of efficacy of source data verification, SDV cannot be the focus and measurable metric of onsite monitoring. Drug developers should design an onsite monitoring strategy around monitoring the compliance of critical processes and integrity of critical data. The conduct of central monitoring will then complement and support onsite activities, reviewing the data to enable the onsite monitor to focus on critical processes and compliance. Study teams should communicate the results of each type of monitoring and drive the focus of the other. As an example, an onsite monitor may identify data quality issues with source data related to labs and the central monitor would target this site and labs in their central review. Conversely, the central monitor may identify discrepant concomitant medications, indicating unreported medical history or adverse events, and ask the onsite monitor to investigate these findings further.

Root cause analysis of findings is an essential part of the early phase central monitoring process as it actively prompts the adaptation of the monitoring strategy to effectively prevent the recurrence of noncompliance. Without root cause analysis, it is not possible to implement effective preventative strategies.

# Holistic Monitoring

Effective monitoring strategies unite not only the onsite and central monitoring team but also include other functional areas such as medical monitoring and data management. Open communication and knowledge sharing facilitates a holistic method of ensuring participant safety and data integrity, reduces silos, increases the speed of data cleaning, and enables optimal conditions for expeditious database lock. Monitoring is a collaborative approach and should include collaboration and communication with medical monitoring, data management, and risk management. Additionally, tools, analysis, and visualizations in the central monitoring platform create effectiveness and efficiencies in the conduct of medical review, data management, and risk management.

# Conclusion

A robust central monitoring strategy, utilizing both onsite and central monitoring methods, is the most reliable and effective way to enhance quality in early phase clinical trials by enhancing the proactive identification of potential issues with participant safety and data integrity. Implementing central monitoring into early phase clinical trials increases confidence in trial quality, minimizes the time required to reach data base lock, and reduces the significant resource impact of late identification of issues, quality event escalation, and the conduct of rework. Simply said: Central monitoring creates quality clinical trials.

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