RISK-BASED MONITORING
Can You Afford to Wait?
Introduction

On-site monitoring is one of the largest cost drivers in a trial, accounting for 30 percent on average of the cost of a clinical trial. Fifty percent of the cost of on-site monitoring involves ensuring data quality through source document verification (SDV). In a time when the pressure is on clinical operations to lower development costs and improve outcomes, the life science industry spent $7.5 billion in 2014 on SDV. Nevertheless, industry and regulatory leaders still express concern that traditional monitoring does not sufficiently evaluate the quality of study data. While significant resources are spent to verify that the source data matches the captured data, traditional monitoring processes often fail to focus on the bigger issues of data quality and protocol violations.

Figure 1: Cost breakdown for a large, global clinical trial (14,000 patients, 300 sites)

“The TransCelerate recommended approach...has shown that SDV is not the best method for managing quality in clinical trials. TransCelerate can now confidently move ahead in our RBM approaches, which use meaningful and valuable monitoring methods, including central monitoring and SDR, to focus on what matters most to the study.”

– Nicole Sheetz, RBM Workstream participant for TransCelerate and Advisor, Clinical Innovation and Implementation, Eli Lilly and Company
Impact of Traditional Monitoring

Today’s monitoring practices are costly, inefficient and do not guarantee quality. In a recent study, Transcelerate Biopharma, Inc. used robust operational data to explore the relative contribution of SDV—the process whereby data within a case report form (CRF or electronic CRF) is compared to the original source of information—to overall clinical data quality. Results of the analysis revealed that only 1.1 percent of total site-entered eCRF data are corrected as a result of SDV, confirming that SDV has minimal impact on overall data quality. This finding supports the conclusion that SDV should not be the primary data quality control method used in clinical trials.

In the traditional monitoring process, subjects are undifferentiated from one another with regard to data quality, operational site performance, safety risks and protocol compliance. The same applies to sites—all are treated identically. This leads to the mindset of, “We don’t know where to focus, so let’s check everything, everywhere, every time.” This approach is inefficient and ineffective, as site monitors spend an inordinate amount of time on low-value, “heads down” activities.

The increasing complexity of trials exacerbates these inefficiencies and increases on-site monitoring costs, as this practice is frequency-based, conforms to a prescribed monitoring visit schedule, and provides generalized quality control at investigational sites. What’s more, the approach still fails to address issues that lead to study delays and poor data quality:

- Inefficient use of monitoring resources and high travel costs
- Study delays related to subject enrollment & database lock
- Impaired ability to remediate data quality issues that can lead to regulatory findings

Although current practice provides a measure of control, it is expensive and does not guarantee data quality. Today there are alternatives. Advances in technology and risk-based monitoring offer the opportunity for a more holistic and proactive approach by combining off-site and central monitoring with targeted on-site monitoring. Efficiencies can be gained without impacting subject safety by implementing quality risk management approaches to clinical trial oversight.
A New Approach Using Risk-based Monitoring

TransCelerate’s recommended methodology for risk-based monitoring (RBM), published in November 2014, highlights that a shift away from conventional on-site monitoring methods is warranted. This shift centers on the belief that centralized monitoring will be better able to identify emerging risks through real-time review of important study parameters. A centralized process for risk detection is more effective because resources will be looking at real-time data rather than waiting to go on site to perform traditional monitoring activities. This philosophical shift in monitoring processes employs centralized and off-site mechanisms to monitor, and adaptive on-site monitoring to further support site processes, subject safety and data quality. By building quality and risk management approaches into the scientific design and operational conduct of clinical trials, risks can be mitigated and issues can be detected early or prevented entirely.

One way to implement the necessary RBM strategy is to follow a four-step, closed-loop, adaptive process (Figure 2).

1. **Create targeted monitoring plan.** In the planning phase, you want to define the optimal targeted monitoring strategy. This involves assessing risks, identifying key risk indicators (KRIs) and defining the important data to create a tiered monitoring design plan, and then allocating the subjects.

2. **Execute.** Once the targeted monitoring plan is complete, the execution process begins. A monitoring checklist enables collaboration with on-site and remote monitors. Using patient profiles and centralized statistical analysis, you can see a real-time longitudinal view of ongoing activities at the patient, site and study level. Using pattern recognition algorithms, central monitors can analyze and discover previously unidentified risks. Central monitors and study managers use these tools to collaborate with the on-site monitors.

3. **Analyze.** In the analysis process, big data analytics can aggregate and analyze all data and automatically derive customized KRIs for each study. This process uses study data to localize risks and continuously adapts to the data as it accrues.

4. **Adjust.** As a result of having a closed-loop solution we can take corrective actions to optimize the outcome. After finding the error rate we can adjust our monitoring plan up or down based on the risks that emerge.

“Increasing use of electronic systems, and improvements in statistical assessments, present opportunities for alternative monitoring approaches that can improve the quality and efficiency of sponsor oversight of clinical investigations.”

– FDA Guidance for Industry
Impact of Risk-based Monitoring

Medidata’s early research proves an RBM approach can lead to faster trials at lower cost and reduced risk. An investment in centralized monitoring capabilities can deliver:

- Fewer on-site monitoring visits, therefore lower travel costs.
- Faster subject enrollment, faster and more reliable decision-making, and faster time from last patient last visit (LPLV) to database lock.
- Heightened ability to identify and remediate risk, improve site performance and data quality, and thus reduce the probability of regulatory findings.

Using a centralized monitoring approach, customers can reduce the number of site visits and associated costs. Monitoring plans may also be adjusted or changed to reduce monitoring costs by 20-30 percent by minimizing visits to low-risk sites while maintaining a frequent visiting schedule for higher risk sites. In addition, data quality can actually be improved while reducing monitoring costs (Figure 3).

This approach augments traditional on-site monitoring with centralized monitoring, centralized statistical analytics and remote visits. Centralized statistical analytics includes anomaly detection, fraud detection, and pattern detection. KRIs include study and site operational parameters such as query rates, data entry cycle time, and early termination rate. These capabilities enable differentiation between sites and between subjects regarding their data quality, operational site performance, known and unknown safety risks, and protocol compliance.

Shifting monitors’ mindsets to “We know where to focus, so let’s concentrate on what’s critical” allows monitors to be more efficient and precise. Monitors can now shift their time from low value, “heads down” activities to higher value activities, such as forging stronger relationships with sites and instilling best practices.

Figure 3: Impact of risk-based monitoring on SDV level
Top 3 Questions You Should Ask

1. Are you concerned with the amount of time and cost that it takes to conduct on-site monitoring?
2. Do you feel your resources are spending too much time on low value tasks and not enough time on important high value tasks?
3. Are you apprehensive about the number of under-performing, under-enrolling sites you have and their impact on your results and costs?

If you have answered yes to any of these questions, it’s time to call Medidata and talk about this new approach to risk-based monitoring. Medidata RBM provides the fastest way to achieve the cost, speed and quality/risk benefits of RBM.

About Medidata

Medidata is the leading global provider of cloud-based solutions for clinical research in life sciences, transforming clinical development through its advanced applications and intelligent data analytics. The Medidata Clinical Cloud® brings new levels of productivity and quality to the clinical testing of promising medical treatments, from study design and planning through execution, management and reporting. We are committed to advancing the competitive and scientific goals of global customers, which include over 90% of the top 25 global pharmaceutical companies; innovative biotech, diagnostic and device firms; leading academic medical centers; and contract research organizations.

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2. Monitorforhire.com annual survey 2013
4. TransCelerate Position Paper on Risk-Based Monitoring, November 2014
5. Medidata Insights Metrics Warehouse