Risk-Based Monitoring of Clinical Trials: An Integrative Approach

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ABSTRACT

Purpose: Clinical trial monitoring is an essential component of drug development aimed at safeguarding subject safety, data quality, and protocol compliance by focusing sponsor oversight on the most important aspects of study conduct. In recent years, regulatory agencies, industry consortia, and nonprofit collaborations between industry and regulators, such as TransCelerate and International Committee for Harmonization, have been advocating a new, risk-based approach to monitoring clinical trials that places increased emphasis on critical data and processes and encourages greater use of centralized monitoring. However, how best to implement risk-based monitoring (RBM) remains unclear and subject to wide variations in tools and methodologies. The nonprescriptive nature of the regulatory guidelines, coupled with limitations in software technology, challenges in operationalization, and lack of robust evidence of superior outcomes, have hindered its widespread adoption.

Methods: We describe a holistic solution that combines convenient access to data, advanced analytics, and seamless integration with established technology infrastructure to enable comprehensive assessment and mitigation of risk at the study, site, and subject level.

Findings: Using data from completed RBM studies carried out in the last 4 years, we demonstrate that our implementation of RBM improves the efficiency and effectiveness of the clinical oversight process as measured on various quality, timeline, and cost dimensions.

Implications: These results provide strong evidence that our RBM methodology can significantly improve the clinical oversight process and do so at a lower cost through more intelligent deployment of monitoring resources to the sites that need the most attention. (*Clin Ther.* 2018;■:1–9)

Key Words: clinical informatics, RBM, risk-based monitoring, statistical monitoring, Xcellerate.

INTRODUCTION

Until recently, the standard approach for clinical site monitoring involved routine on-site visits at a prescribed frequency applied uniformly across sites regardless of their level of risk and relying heavily on source data verification (SDV) as a means to ensure data quality and patient safety. However, there is mounting evidence that SDV is far less useful than originally thought[1–5] and can be reduced by >90% (and altogether eliminated for large studies) without any measurable impact on data quality.[6] The vast majority of data errors identified through SDV are random in nature and evenly distributed across sites and treatment groups and can be caught using standard edit checks and statistical approaches.[6] Indeed, a recent analysis of site monitoring reports revealed that centralized monitoring activities could have identified 95% of the findings of on-site monitoring visits, <1% of which were critical or major in nature.[7]

These observations have led regulatory agencies and industry consortia, such as TransCelerate, to embrace a risk-based monitoring (RBM) methodology that

Accepted for publication April 28, 2018.
https://doi.org/10.1016/j.clinthera.2018.04.020
0149-2918/$ - see front matter

combines centralized and off-site review of important study parameters with an adaptive on-site monitoring approach that places greater emphasis on risk-mitigation activities, such as Good Clinical Practice, source data review (SDR) and training.[8–12] In essence, RBM separates *critical data* from *critical processes* and provides a framework that allows site monitors to prioritize the high-value task of compliance checks over the low-value task of fixing transcription errors, which can be detected much more reliably and efficiently using computer-based techniques, such as edit checks and statistical monitoring.[13]

TransCelerate research advocates that an optimal RBM system should excel in the areas of risk assessment and cross-functional risk mitigation planning, data integration, risk indicator data review, and risk and issue tracking, management, and analysis.[10] A number of commercial and home-grown solutions have been developed, which vary greatly in sophistication and completeness. Medidata's Strategic Monitoring suite[14] includes a dedicated solution for risk assessment and planning, whereas key risk indicator review is integrated into their Centralized Statistical Analytics tool that also provides data anomaly detection using statistical techniques. In addition to these centralized monitoring tools, Medidata's suite includes modules for targeted SDR and SDV, along with a cross-functional issue management and workflow module. However, one of the key limitations of Medidata's monitoring suite is its tight coupling with their electronic data capture product. The RBM solution from CluePoints includes a risk assessment and categorization tool, a key risk indicator dashboard and statistical techniques to detect data quality issues and outliers, and a built-in issue management system.[15] CluePoints' solution integrates with Oracle's InForm and Medidata's Rave but lacks comprehensive data integration capabilities. Other commercial solutions from PerkinElmer,[16] Cognizant,[17] BioClinica,[18] and eClinical Solutions[19] are more limited in their capabilities and are mostly focused on key risk indicator review. Several clinical research organizations, such as IQVIA,[20] Paraxel,[21] ICON,[22] TRI,[23] and Cyntegrity,[24] have internally developed solutions with varying capabilities, and there have been numerous conference presentations on the use of data visualization tools to facilitate the identification of high-risk sites and subjects. However, many of these tools are isolated from operational workflows and lack the integrations that are necessary to enable a frictionless user experience.

Both our own work in discovery,[25] clinical,[26,27] and outcomes research[28] and work in other scientific domains[29] have found that human intuition married to meaningful and *actionable* visualizations can lead to more optimal outcomes than a purely statistical or computational approach. Our primary goal in designing our RBM solution was to allow clinical staff who may not have formal training in data mining, informatics, or statistics to readily identify patterns in the data, confirm or challenge their assumptions, and make more informed decisions.

PROCESS

Our methodology is centered on the three cornerstones of a risk-based approach to monitoring clinical trials: quality by design, central monitoring, and triggered, adaptive on-site and remote monitoring.

Quality by Design

Our quality-by-design process steps include protocol review, study risk assessment that includes subject participation and data flow mapping, initial site risk assessment and selection, critical data and process definition, and RBM plan development.

Central Monitoring

Central monitoring is the process of reviewing aggregate data from an ongoing trial using analytics and visualizations to identify poorly performing investigational sites, detect unusual patterns in patient- and site-level data, predict potential issues, mitigate areas of risk, and correct problems in the execution of a clinical trial. Central monitoring also includes the management of findings and issues identified throughout this process in a holistic manner.

Adaptive, Triggered On-site and Remote Monitoring

Our adaptive, triggered monitoring processes are used during the subject enrollment and study maintenance phases of a trial and include reduced levels of SDV, SDR, and on-site monitoring, increased levels of remote monitoring, and triggered monitoring activities. Our central monitoring methodology uses a top-down approach to identify and manage risks at the data point, visit, subject, site, country, and study levels. To enable comprehensive evaluation through different reviewer lenses, we