Risk-Based Monitoring: A Cognizant Approach

NAMSA Risk-Based Monitoring Working Group: Therese Everson, MBA; Sharon Herbert, PhD, MBA; Jennifer Mischke, MPH; Tyson Rogers, MS; Katie Schaaf, MS; Jill Visor, MS

Clinical & Consulting

NAMSA Whitepaper #17 08/2015
Introduction
Conducting clinical trials in today’s environment of evidence-based data requirements combined with reduced funding and day-to-day budget constraints is forcing Sponsors and CROs to take a more efficient approach to implementing and managing their clinical studies. These aspects, along with FDA’s guidance document on risk-based monitoring and the European Medication Agency’s (EMA) reflection paper on risk-based quality management in clinical trials, has lent momentum to a movement that addresses one of the most expensive budget line items—clinical trial monitoring—in creative ways, including risk-based monitoring. The most effective means of implementing a risk-based monitoring (RBM) system requires a cognizant and thorough approach from the beginning of the trial that entails continually assessing data integrity and patient safety at the study and site level by leveraging technology and tools, as well as intellect and resources from all members of the clinical study team.

Global Guidance and Perspectives on Risk-Based Monitoring
In August 2013, FDA released a guidance on risk-based monitoring, which was followed later that year by an EMA reflection paper on risk-based quality management. These documents came shortly on the heels of a similar release supporting risk-based monitoring in Japan and nearly 2 years after the UK released its own guidance on the subject. These guidance documents and position papers take the medical device industry a step closer to formalizing RBM approaches, adding to the growing consensus that in the future, RBM may well supersede the historically more traditional on-site monitoring.

FDA recommends a “quality risk management” approach to clinical trials and is considering the need for additional guidance describing this approach. Points FDA will consider:

- “Quality is an overarching objective that must be built into the clinical trial enterprise”
- There is a growing consensus that risk-based approaches to monitoring are more likely than routine on-site monitoring visits (with 100% data verification) to ensure subject protection and overall study quality
- Findings suggest that certain data anomalies may be more readily detected by centralized monitoring (remote evaluation of the study) than by on-site monitoring
- Recent review of on-site monitoring data determined that centralized monitoring activities could have identified >90% of the findings identified during on-site monitoring
- There needs to be a focus on the suitability and accuracy of the data collected and the safety of all participants involved
The EMA reflection paper provides key aspects to be considered when implementing a clinical study in order to ensure sufficient information is gathered to support good decision making, or “fitness for purpose.” The risk-based approach to monitoring falls nicely into this strategy of clinical study conduct. Several of the aforementioned guidances discuss risk assessment, risk control, and risk review as well as tolerance limits; and all mention the potential impact of implementing a centralized monitoring approach.

**The Recommended RBM Philosophy**

Risk-based monitoring is defined as a method of monitoring a clinical trial by identifying risks to patient safety and data quality and then tailoring monitoring methods to address those risks. By taking a targeted approach to monitoring, and using the tools and resources available to the Sponsor and/or CRO (i.e., biostatisticians, data management reports, and the clinical trial management system [CTMS]), the study’s monitoring budget can be reduced (fewer visits, less travel) while still maintaining the integrity of the study data and results. The RBM philosophy is summarized in three key facets:

1. **Take a cognizant and thorough approach to creating and implementing global tools and strategies**

   Whether or not you are following FDA regulations, ISO 14155, or any other global clinical trial requirements, you must have specific documents saved in your trial master file and tools in place to effectively implement RBM for your study-specific needs. Assessing and documenting the acceptability of assuming a certain level of study risk for your monitoring strategy via a Study Risk Profile (SRP) (Figure 1) is essential to demonstrating that the study is appropriate for the RBM approach. The Centralized Data Monitoring Plan (CDMP) (Figure 2) or a similar formal study document must proactively define alert/alarm levels and the mitigations for your risks throughout the study. Low/Moderate/High risk categories should be assessed and revised as needed over the course of the trial. The study-specific Risk-Based Monitoring Plan (RBMP) (Figure 3) and CDMP reference the SRP, and all three documents work interactively to help you manage your monitoring resources and needs effectively.

“By taking a targeted approach..., the study’s monitoring budget can be reduced (fewer visits, less travel) while still maintaining the integrity of the study data and results.”
2. Apply an interactive approach to continually assess the data integrity and patient safety at the site and study levels

Through routine interactions with research sites, collection of subject data in the electronic data capture (EDC) system (e.g., adverse event information, rates of critical deviations, time to query closure, etc), and site data in the CTMS (e.g., Principal Investigator oversight, coordinator responsiveness/engagement, etc), you have an abundance of readily available data to leverage for implementing RBM in any clinical trial. An RBM dashboard (Figure 4) and statistical reports are developed at the start of the trial, and are updated as data are collected. Both subjective and objective data are incorporated in the statistical reports and summarized to create the RBM dashboard. Typically, a cross-functional team (i.e, project manager, monitors, biostatisticians, data managers) reviews the dashboard and metrics monthly throughout the enrollment phase and quarterly through long-term follow-up, or at more appropriate intervals based on enrollment rates and follow-up visit requirements. Sites with metrics that trigger on-site visits, or fall onto the “watch list” for potential action, are reviewed more frequently, if needed.

3. Utilize technology, cross-functional tools, intellect, and resources to provide easy-to-use reports for risk-based monitoring

You may already have the tools and resources in place to implement your RBM strategy. Bringing them all together at the appropriate time with the right cross-functional team members is critical. Statistical programmers and biostatisticians use both simple and highly complex modeling methods to review the study data from multiple perspectives. This group collaborates with the data management team to develop centralized monitoring reports and implement the RBM dashboard for each study.

The project manager and monitoring experts, with their extensive site-specific knowledge,
“You may already have the tools and resources in place to implement your RBM strategy. Bringing them all together at the appropriate time with the right cross-functional team members is critical.”

use these reports and models to target sites in need of additional training or on-site monitoring, and document these decisions to effectively support the approach at the time of a regulatory body inspection.

NAMSA has the experience, resources, processes, and systems in place to meet your risk-based monitoring needs. NAMSA has developed tools and templates to get your study started on the right foot. Watch for future information from NAMSA regarding the following RBM topics:

- Key considerations in developing and maintaining your SRP and other RBM-specific documents
- Considerations for clinical implementation of RBM
- Data management tools and integration tips
- The site perspective of RBM and remote monitoring
- Clinical quality/oversight of RBM implementation (to ensure that your study can hold up to regulatory body inspections, both at your research sites and of the Sponsor/CRO)
- Case studies with real-world examples of RBM implementation.
“NAMSA has the experience, resources, processes, and systems in place to meet your risk-based monitoring needs.”

REFERENCES


About the Authors

The NAMSA Risk-Based Monitoring (RBM) Working Group is a cross-functional team with an average of 15 years of experience per member in designing, implementing, monitoring, auditing, and analyzing all aspects of global medical device trials. The RBM Working Group is responsible for developing, supporting, and overseeing NAMSA’s RBM program, and has developed RBM tools in support of studies ranging from regulated pre-market to post-market registry studies conducted around the world. The RBM Working Group consists of Therese Everson, MBA, Senior Principal Medical Research Manager, Quality Services; Sharon Herbert, PhD, MBA, Medical Research Manager, Clinical Services; Jennifer Mischke, MPH, Director of Biostatistics and Data Management; Tyson Rogers, MS, Principal Medical Research Biostatistician; Katie Schaaf, MS, Director of Strategic Partnering Operations; and Jill Visor, MS, Director of Clinical Research.
“Everything we do must be in our clients’ best interests.”

Ted Gorski, NAMSA Founder

Throughout our almost 50-year history, NAMSA has assisted thousands of companies around the world in translating their great ideas into medical products for the patients who need them most.

Our regulatory strategy, testing services, quality system consulting, clinical research, and sterilization products support the medical product development process. With NAMSA’s MRO® approach to testing and consulting, you maintain project control while gaining the benefit of on-demand external support: extending your in-house capabilities, accessing specialized expertise at exactly the right time, or having a completely outsourced development process.