Risk-Based Monitoring: Setting up the Structure for a Systematic Approach

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Introduction
The success of your clinical study is dependent on many factors, but one of the most crucial is a comprehensive plan, developed through careful consideration of study objectives and potential pitfalls. From protocol development to site selection, a design that leads to optimum participant safety and quality data requires a methodical approach with active participation from experts on a multi-disciplinary team. This is perhaps most essential when you are planning to conduct a study utilizing Risk-Based Monitoring (RBM). In fact, though RBM may be seen as a method of reducing major costs over the life of a study, successful RBM will necessitate additional resources be utilized up-front. Beginning with a thorough risk assessment to identify and quantify the particular risks of the study and determine whether RBM is appropriate, sponsors, clinical project managers, biostatisticians, and data management personnel work together to set the stage for a quality study. When RBM is found to be justified, utilizing cross-functional expertise and a reliable, proven method of conducting the study should result not only in efficiency and saved resources in the long-run, but also in quality that equals or surpasses that of a traditional approach. This is due to RBM’s focus on risk management, which is intended to reduce the impact of risk to acceptable levels by proactively identifying and tracking issues, and addressing them effectively to prevent undesirable consequences. RBM requires energy and resources to be highly focused on the essentials — a clean, targeted, and intelligent approach.

As discussed in “Risk-Based Monitoring: A Cognizant Approach”, the first white paper in NAMSA’s RBM series, NAMSA has developed a systematic approach to RBM that aligns with recommendations from key guidance documents and position papers, namely FDA’s guidance document on risk-based monitoring and the European Medicines Agency (EMA) reflection paper on risk-based quality management in clinical trials. NAMSA’s RBM philosophy involves taking a cognizant and thorough approach to creating and implementing global tools and strategies, applying an interactive approach to continually assess the data integrity and patient safety at the site and study levels, and utilizing technology, cross-functional tools, intellect, and resources.

This white paper will explore four template documents and their processes which are specially designed to support these concepts and a successful RBM study:

- Study Risk Profile (SRP) — defines risks of the clinical study, assesses the study for its suitability for implementing RBM, and provides a recommendation for the allowable extent of RBM.
- Risk-Based Monitoring Plan (RBMP) — describes the RBM strategy and monitoring activities for the study, and facilitates regulatory compliance.
- Centralized Data Monitoring Plan (CDMP) — details the manner of on-going review of study data summaries and reports, and specifies thresholds that will trigger additional monitoring activities.
- Periodic Review of RBM Site Metrics (Dashboard) — displays metrics as defined in the CDMP for the purpose of on-going review of identified risks, and informs decisions to escalate issues and/or modify the monitoring strategy.

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These documents serve as a framework upon which study decisions are documented, justified, and communicated within the cross-functional team as well as to any regulatory body. In the planning stage of a study, these documents are customized to fit the unique characteristics of the study. The template documents walk you through important considerations for an RBM study while remaining flexible enough to allow adjustment in the face of unforeseen factors arising during the study and new observations and data.

**Study Risk Profile**
Not every study is an appropriate candidate for RBM. A thorough risk assessment should be performed to ensure that RBM does not result in significant increases in risk to the safety of participants or data quality. This is done through the completion of a Study Risk Profile (SRP). The SRP serves to guide the sponsor and team in quantifying study risk using criteria developed from regulatory requirements and experts in clinical study design.

Through the SRP development process, NAMSA’s team of experts and key sponsor representatives consider a range of issues in determining level of risk. The risk of the investigational device itself is first explored and determined to be of low, medium, or high risk compared to standard medical care for the indication. Additional areas are rated in this manner and include:

- Novelty of study device, treatments, and/or procedures;
- Complexity of the study design;
- Medical complexity of the study population;
- Expected rate of enrollment and volume of data;
- Severity and rate of expected adverse events;
- Complexity of inclusion/exclusion criteria; and
- Previous experience and compliance history of investigators and site staff.
With risk levels identified, the team will determine whether the benefits of RBM outweigh potential study risks. This may be the case if the risks are primarily rated as low, or if a targeted monitoring strategy could effectively address medium and high risk areas. If the team determines that RBM is warranted, they then establish an acceptable level of monitoring. Depending on the nature and severity of identified risks, the monitoring strategy could involve source document verification (SDV) of a reduced subset of data for all participants, SDV of a reduced number of participants and/or a reduced subset of data for those participants, or no SDV. A strategy could also be applied to the study as a whole, or broken down on a site by site basis (e.g. 100% SDV for sites a, b, c, and reduced SDV for sites x, y, z). The final SRP document will serve as justification of the method for regulatory bodies as well as the scientific community.

The SRP becomes a guide to designing the monitoring method to target the most resources and most stringent monitoring to the highest risk areas, and allows risks to be tracked throughout the study, resulting in issues being addressed and resolved early and effectively. The subsequent RBMP and CDMP detail the particular monitoring methods to be employed.

Risk-Based Monitoring Plan

In a traditional study, where often 100% of participants and data are source document verified, the monitoring plan typically includes standard descriptions of the monitors’ responsibilities as well as the timing and frequency of on-site monitoring visits. A monitoring plan serves as a guide for monitors in their responsibilities to verify that the rights and welfare of human subjects are protected, data is accurate and source data verified, and the study is conducted in compliance with the protocol and regulations. Due to the unique nature of an RBM study and the potential for variable and complex monitoring methods being employed, a Risk-Based Monitoring Plan (RBMP) requires additional detail to document how these responsibilities will be met.

The following are key elements of the plan that require careful consideration:

- **Risk mitigation** — The RBMP will review the critical risks identified in the SRP and explain the RBM strategy that will be employed to mitigate those risks. Methods to support this, such as targeted source data verification and remote monitoring, will be identified.

- **Site initiation visits** — In addition to the activities required of a traditional clinical study, emphasis should be placed on prevention of events that were identified as high risk in the SRP. Monitors will be required to discuss the unique monitoring requirements and expectations for the RBM study with study personnel. Special attention should be given to sites and staff that are inexperienced or unfamiliar with RBM. Logistical information should be gathered regarding the transmission of source document copies to the monitor if remote visits are anticipated. The site’s ability to mail, scan, or upload redacted copies of source documents should be assessed given the site’s technology and the IRB/REC policies. Remote electronic access should be explored with the site.

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Interim monitoring visits — The plan will clearly define on-site and remote monitoring activities that will occur throughout the study. If remote visits are anticipated, clear instructions should be given on how these will occur and should include:

- The method of obtaining copies of source documents — The preferred method should be described as well as alternatives in case a site is unable to adhere with the first option.
- Document disposition in-house — The method of storing or destroying copies of source documents, whether they are received via email, mail, or fax, should be described.
- Informed Consents — Methods of maintaining confidentiality during monitoring and methods of document destruction should be documented for Informed Consents.

Timing and frequency of monitoring activities — this is dependent on the nature and timing of these critical risks. For example, if the study protocol is exceptionally complex, more monitoring resources would be allotted to site initiation and first interim visit, with ample time allowed for training. Timing requirements for on-site versus remote visits should be distinguished.

Data to be source verified — The RBMP will outline the critical data points to be source data verified as a percentage of data across all subjects, a percentage of subjects, or a combination of the two. For example, Informed Consent forms may be verified for 100% of subjects, but critical data points verified for 30% of subjects. The chosen approach will employ a sampling technique to select specific subjects, and specific data points, to be monitored during an on-site visit or remotely.

Centralized Data Monitoring Plan
Centralized data monitoring refers to the utilization of data listings and summaries, derived from the study database, to identify errors and anomalies that may require follow-up with the site. The study database, which contains data from all participating sites, can be invaluable in identifying data trends across sites, as compared to source document verification which focuses at the individual subject level. If a site shows overall higher or lower results for a key variable, such as adverse event rates, protocol deviation rates, or procedure duration, it may indicate the site requires follow-up such as additional training and/or on-site monitoring. Centralized data monitoring may be conducted by clinical, data management, and/or biostatistics personnel. Responsibilities should be determined based on the unique characteristics of the study with the intention of maximizing efficiency and quality.

Though certainly utilized in traditional studies, centralized data monitoring plays a particularly key role in mitigating the risks in an RBM study. The Centralized Data Monitoring Plan (CDMP) in an RBM study not only describes how and when data will be reviewed during the study, but also defines thresholds which, when met, trigger additional monitoring actions such as increased on-site monitoring or escalation of potential issues at an investigational site. Thresholds are governed by the risks identified in the SRP.
Hitting a threshold would trigger a predetermined response. For example, if particular types of protocol deviations are determined to be a high risk in the SRP, the CDMP will identify a cap for the number of deviations per site and for the study as a whole, at which point additional monitoring and training would be justified.

**Periodic Review of RBM Site Metrics**

Through the use of well-designed Electronic Data Capture (EDC) and Clinical Trial Management System (CTMS) software, reports can be run in real-time that are customized to efficiently deliver the most suitable information in the form of a Periodic Review of RBM Site Metrics (Dashboard) which is reviewed jointly by the study statistician, data manager, and Medical Research Manager. The Dashboard will display objective study data, pulled from EDC, in the areas of risk identified in the SRP. Examples include rate of critical deviations reported, rate of Case Report Form (CRF) completion, and rate of adverse events. Also displayed are results of monitor questionnaires which may provide subjective feedback on site performance measures such as Investigator involvement and site compliance. In this manner, the expertise of the entire study team is leveraged and communicated cross-functionally. This collaborative review process is the mainstay of an effective RBM study.

Objective and subjective data for each site is listed on the Dashboard. Values falling at or above the threshold, as pre-determined in the CDMP, will be flagged as yellow or red respectively. Based on this, the review team will determine an action plan for each site. Action levels are pre-defined as well and may include a call with the Primary Investigator and/or Coordinator, an additional on-site monitoring visit, or other appropriate escalation. Sites with no flagged items are determined to require no action, and sites that are approaching threshold may be put on a “watch list” which is maintained via the Dashboard. Results from each review are recorded and revisited at the subsequent review. Action items specific to each site are assigned by the review team and tracked as well. Examples of additional action items might be for a monitor to review a site’s training records, or for data management personnel to report additional metrics for a particular site.

**Living Documents**

Flexibility is a fundamental characteristic of RBM. Through regular review of the Dashboard, issues are identified and addressed by modifying monitoring activities. The SRP, RBMP, CDMP, and Dashboard are living documents, intended to be revised as the need arises. However, this should not lead to an inordinate amount of additional work and non-essential retraining. These documents are designed in such a way that they work in parallel with other major study documents (e.g., training plans, monitoring reports, project plan), but a change in one will not guarantee a change to all others.

The interaction of the documents and interrelatedness of study personnel are represented in Figure 1. Blue arrows show the manner in which the initial SRP informs the monitoring strategy. Orange arrows depict the feedback loop created through on-going dashboard review by the cooperative team.
Utilizing RBM can seem like a daunting task given the high stakes of a clinical study. However, by exercising a systematic approach, you can achieve high efficiency and a level of quality that matches or exceeds that of a traditional monitoring strategy. Performing a thorough risk assessment will bring priorities into focus, and the resulting SRP will serve as the backbone that supports the study’s monitoring strategy. A cross-functional team of experts, able to employ sophisticated tools and resources, can develop an RBMP and CDMP to efficiently mitigate identified risks. NAMSA’s expertly designed approach and comprehensive template documents provide a path to successful RBM study implementation and results.
REFERENCES


About the Authors

The NAMSA Risk Based Monitoring (RBM) working group consists of Therese Everson, MBA (Sr. Principal Medical Research Manager – Quality Services), Sharon Herbert, PhD, MBA (Medical Research Manager – Clinical Services), Jennifer Mischke, MPH (Director of Biostatistics and Data Management), Jodi Mullin, MSW, CCRA (Senior Medical Research Associate), Tyson Rogers, MS (Pr. Medical Research Biostatistician), Katie Schaa, MS (Director of Strategic Partnering Operations), and Jill Visor, MS (Director of Clinical Research). This cross-functional team has a combined average of 15 years of experience 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.