Introduction
You have gathered your team of experts, identified your study’s areas of greatest risk, and developed a monitoring plan to address those risks, setting you up for a successful study utilizing risk-based monitoring (RBM). With this thorough Risk-Based Monitoring Plan (RBMP) in hand, are your clinical personnel ready to hit the ground running?

Guidance from the U.S. Food and Drug Association (FDA)\(^1\) and the European Medicines Association (EMA)\(^2\), as well as recommendations from the United Kingdom\(^3\) and Japan\(^4\) all encourage the use of alternative approaches to monitoring investigational sites and emphasize the dynamic nature of the RBMP. Monitoring strategies for RBM studies can be complex and novel for sponsors, CROs, and sites. A combination of on-site, remote, and centralized monitoring will likely be included in the plan. There are a number of elements to consider beyond the monitoring plan in order to facilitate proper trial execution, ensure subject protection, and attain quality data.

The first two white papers in NAMSA’s RBM series, “Risk-Based Monitoring: A Cognizant Approach”\(^5\) and “Risk-Based Monitoring: Setting up the Structure for a Systematic Approach”\(^6\), describe NAMSA’s philosophy and systematic approach to RBM—an integrated model involving risk assessment, justification of the risk-based approach to monitoring, and the development of a highly customized monitoring strategy. Utilizing a wide variety of sophisticated data monitoring methods, a cross-functional team of experts review and address risk real-time throughout the study. Monitoring with intense focus on high-risk areas aims to prevent, identify, and address issues early and effectively. A Risk-Based Monitoring Plan (RBMP), Centralized Data Monitoring Plan (CDMP), and Periodic Review of Site Metrics (Dashboard) are developed based on the original Study Risk Profile (SRP). With these well-developed roadmaps created, the discussion turns to implementation. The importance of preparing and supporting clinical personnel and investigative sites cannot be overlooked. Giving an appropriate amount of attention to the process and using the right tools at the right time will mitigate potential errors in the conduct of the study, help your internal team and site personnel navigate RBM, preserve essential relationships, and strengthen partnerships with sites. This white paper will discuss key considerations for RBM study implementation and provide suggestions on ways to ensure success internally, within the study team, as well as externally, with the study investigators and site staff.

Preparing for success
RBM strategies call on monitors and in-house clinical research associates (CRAs) to employ a variety of monitoring activities in a structured, purposeful manner. On-site monitoring may be supplemented with centralized and remote monitoring. Centralized 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;
while remote monitoring refers to the performance of activities typically associated with on-site visits—e.g., source document verification (SDV) and investigator file review—remotely, off-site through teleconference, email, study databases, or other technologies. Though centralized and remote monitoring have been used to varying degrees in traditional clinical studies, they are an integral part of an RBM strategy. The risk-based approach requires a change in mind-set that may not be as simple as following the steps prescribed by SOPs and monitoring plans. Conceptually, clinical personnel are asked to let go of the focus on each individual data point in favor of a more holistic approach, emphasizing the most important data and highest risk sites. They may be asked to perform tasks that are unfamiliar to them, such as targeting specific subjects and data points for monitoring based on data trends and statistical triggers or based on a randomization scheme rather than reviewing all data from every subject enrolled.

There are several activities that, if conducted prior to selecting and qualifying investigational sites, will save time and money in the long-run. Implementing the suggestions provided here will assist internal team members and equip them to support the RBM strategy with research sites, giving them the tools they need to prevent costly surprises.

**Train CRAs on Risk-Based Monitoring**

It is suggested that training takes place as a team to avoid misunderstanding and inconsistencies between monitors. Discussion should highlight the risks identified in the SRP and the ways in which the monitoring plan is designed to mitigate those risks. As centralized data review is key to the success of RBM, it will be helpful for all team members to understand the key indicators and how often pre-specified site metrics will be reviewed. In addition to the RBMP, CRAs should have an understanding of how the data management and statistical aspects of the monitoring strategy are designed to detect abnormal values and trends and how these analyses and data summaries complement on-site review of specific subject data points. In many cases, feedback from the CRA on the site’s performance is essential information that feeds into the analysis. If a random sample of sites and/or subjects will be identified for increased SDV, the randomization plan and the method in which it is to be employed should be communicated clearly to the monitors. Monitors who have been accustomed to 100% on-site SDV may find the limitations on monitoring activities uncomfortable as they are used to seeing the whole picture and following up on every detail. The FDA guidance on RBM cites a 2012 review of on-site monitoring findings during an international trial that posited that 90% of the findings could have been identified through centralized monitoring. Understanding the overall mechanism for maintaining data integrity and subject safety will assist the team in understanding the capabilities of RBM and help in the transition from 100% SDV.
Determine internal processes

Once site activation is underway, there is little time to spend creating processes or trouble-shooting technical issues. It is suggested that the following elements be considered prior to the start of enrollment:

- Customized Monitoring Report Templates – In addition to an RBMP that clearly defines each type of monitoring activity, customized monitoring report templates for each scenario (e.g., an on-site visit to a site randomized for 100% SDV, or a remote review of a site randomized for informed consent review only) not only provide much-needed guidance for monitors, but also make it very clear to an auditor that the monitoring expectations were met for the particular type of activity. Templates should be annotated to ensure consistency across monitors. Consider including details in a remote monitoring report regarding the method of receiving documents, the specific documents used to verify data, and the disposition of documents after review.

- Test Database – If monitoring activities will include the use of database functions such as source document uploading, provide monitors and in-house data reviewers a test database so they can familiarize themselves with the coordinator’s view and prepare themselves to effectively work through the monitoring process with the research coordinator when not on site.

- Site Training Plan – Have a solid site training plan to ensure thorough protocol training, data entry requirements, and expectations of your study’s RBM strategy, including the procedures and expectations for the research sites to support remote monitoring and targeted monitoring.

- Source Document Transmission—If remote monitoring is included in the RBMP, determine the process for receiving, de-identifying, filing, and/or destroying paper or electronic source documents. This may vary between sites depending on technical capabilities, geographic requirements (e.g. Safe Harbor requirements), or time restraints. Consider the site’s expectations, regulations, and procedures and whether they are able to support remote and/or reduced on-site monitoring, particularly in the case of a global study.

Be pragmatic in site selection

The evaluation process for choosing clinical sites for study participation is a tool for risk mitigation regardless of the monitoring strategy employed. Site selection in a study using an RBM strategy will ideally be guided by the risks identified in the SRP. For example, if one of the highest expected risks is unusually rapid enrollment, it may be best to select sites with more experience, enough resources to ensure timely data entry, and a history of fast enrollment. If sites have been identified prior to the creation of the SRP, the characteristics of those sites become a factor to consider in evaluating the study risks. In either case, keeping in mind that the SRP is a dynamic,
“living” document, there should be an intentional feedback loop between site evaluation and the SRP throughout the selection process. An RBM strategy occasions additional factors to be considered when assessing the suitability of potential investigational sites. If a random sampling of sites and/or subjects will be chosen for SDV, sites will need to be flexible enough with staffing to accommodate potential changes in workload throughout the study. If sites will be expected to perform activities related to remote monitoring, such as sending informed consents and uploading source documents to a secure portal or database, site resources will need to be assessed accordingly. Given the staff’s experience, access to medical records, and technical capabilities, will the site be willing to participate in remote monitoring? Does their Institutional Review Board (IRB) or Ethics Committee (EC) have additional firewalls in place that may prevent the site from effectively supporting the Sponsor’s approach to monitoring? How burdensome is this approach for sites? Do they have a scanner or technical capabilities to convert documents received in paper form to electronic file? The answers to these questions could affect budget negotiations, the Sponsor’s CRA that will be working with the site, and the amount of time that will need to be spent internally to ensure compliance.

Prepare for on-site visits
Fewer, less frequent on-site visits necessitate thorough preparation on the part of the monitor. An on-site visit in an RBM study should be highly focused on tasks that can only be carried out in person. Depending on the capabilities of remote monitoring, this may include reviewing medical history and other available records for adverse events, face-to-face training, regulatory binder review, device accountability, or assessing the ongoing acceptability of the research site for continued participation in the study; not to mention the relationship-building activities that are inherent with face-to-face interactions. The RBMP will outline those activities that must be performed at an on-site visit; however, if a monitor has not reviewed and familiarized themselves with the site’s nuances using the resources
available to them remotely, they may find themselves caught up in details and lose precious time to really address those critical risks identified in the SRP. Internal study team members who have reviewed centralized data monitoring reports, conducted data review, and completed some remote monitoring visits for a site should be consulted prior to an on-site visit. Monitors should be up-to-date on the most recent periodic study review dashboard.

Partner with sites
The relationship between Sponsor/CRO and Investigators and their research teams greatly impacts the success of all clinical trials. A trusting and respectful partnership can impact subject recruitment, the rate at which sites hit key milestones, data accuracy, protocol compliance, and much more. Implementing a non-traditional monitoring method can potentially put a strain on relationships with study sites. As it was with the introduction of Electronic Data Capture Systems, RBM approaches can appear, at least at first glance, as putting a different type of burden on the site. Despite a growing understanding that centralized monitoring practices are capable of identifying the majority of critical errors, site personnel may feel that without the checks and balances provided by monitors’ 100% SDV, greater responsibility is placed into their hands to ensure accuracy of data and adherence to the protocol. Anticipate the concerns sites may have and prepare to address them. This extra attention will strengthen relationships as there will be more opportunity to partner on navigating the complexities of the RBM trial. An upcoming NAMSA white paper focused on the site’s perspective of RBM will take a closer look at some of the issues sites face when implementing and conducting an RBM trial.

Conclusion
As risk-based monitoring (RBM) becomes more clearly defined and routinely utilized, Sponsors, CROs, and sites alike will gain expertise, operations will be stream-lined, and pitfalls will more easily be avoided. In the meantime, it is important that Sponsors/CROs are sensitive to the fact that both internal clinical staff and investigational sites will be challenged to think outside the box. Prudent consideration of clinical study elements that are unique to RBM and awareness of the challenges will prevent process inefficiencies and relationship strains.
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 Schaaf, 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.