Risk-Based Monitoring: Exploring the Clinical Site Experience

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For the past few years, regulatory bodies, industry advocacy groups, and private companies alike have been tackling the concept of incorporating risk into the design of clinical trials and customizing monitoring strategies based on those risks in an effort to achieve higher quality outcomes. Core sources of guidance on the risk-based approach can be considered the European Medicines Agency (EMA) reflection paper and the U.S. Food and Drug Administration (FDA) guidance document, which were first released as drafts for comment in 2011. These documents sparked additional efforts to operationalize this approach to quality management including one of the first initiatives of TransCelerate Biopharma, a non-profit industry consortium formed in 2012, which published a standard methodology in 2013. NAMSA's own proposed method was first described in the white paper “Risk-Based Monitoring: A Cognizant Approach”. However, in the midst of all the buzz about Risk-Based Monitoring (RBM), focus has largely been on defining a Sponsor’s/Contract Research Organization’s (CRO’s) methodologies for risk-assessment and adjusting monitoring activities to address those risks most effectively. It seems less attention has been paid to the impact these new strategies have had on clinical sites that play the role of first line of defense for quality data and patient safety.

The purpose of this white paper is to bring the clinical site’s experience of RBM to light through a review of recent developments and resources focused primarily on clinical research site viewpoints. Drawing from the expertise of industry authorities, including the collective experience of NAMSA’s own clinical personnel, this document will provide recommended methods for Sponsors/CROs to address concerns in an effort to strengthen their partnership with clinical sites, thereby enhancing the quality and functionality of the RBM approach.

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NAMSA Risk-Based Monitoring Working Group
The NAMSA Risk-Based Monitoring (RBM) Working Group consists of 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 (Senior Principal Medical Research Biostatistician); Katie Schaal, MS (Director of Strategic Partnering Operations); Jill Visor, MS (Director of Clinical Research); and Angela Warren, MS (Senior Internal Compliance Specialist). 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.
Site Perspective

In response to the growing popularity of RBM among industry Sponsors, there have been various efforts to gain insight into the effects RBM has on clinical sites and to understand the experience and needs of Investigators in light of changing demands. A discussion paper published in German Medical Science in 2013 reviewed the state of RBM in practice. The authors noted that the implementation of RBM has often overemphasized reduced source document verification (SDV) as the hallmark of the risk-based approach with sites. Though a reduction in on-site SDV is one means of freeing up resources in order to target the most critical data, it does not in itself lead to a meaningful risk-based approach. Poor communication between monitors and sites, as well as between monitors and Sponsors regarding site contact, was also noted for trials using RBM. Site personnel who have experienced RBM as simply reduced SDV and reduced communication may see this monitoring strategy as only a means of saving money for the Sponsor while passing on even more of the burden of responsibility for quality assurance to them.

In 2012, the Society for Clinical Research Sites (SCRS) formed as a non-profit trade organization, giving a voice to research sites. Partnering with the industry forum Linking Leaders, SCRS surveyed site personnel regarding their views on RBM in 2013. Some of the biggest concerns revealed in the survey were increased workload without a change in budget and the need for more internal resources. The SCRS site quality survey conducted in 2014 gives further insight into site concerns in regards to factors that influence quality performance, including Sponsor/CRO behaviors. Among the factors identified as challenging the site’s ability to perform were inconsistent messages from Sponsor/CRO, less face-to-face training, and increased demands.

Professional associations, such as the Association of Clinical Research Professionals (ACRP), began offering RBM courses geared specifically to Clinical Research Coordinators (CRCs) and Investigators in 2013. ACRP identifies several major impacts RBM can have on site personnel, including increased responsibility for sites to ensure timely data entry and data accuracy, a decrease in face-to-face contact with Sponsors/CROs yet a possible increase in the total number of contacts (such as data management and other internal personnel), and a change in elements of the site budget such as timing of payments and activities surrounding increased remote monitoring.

The Japanese position paper on RBM perhaps highlights the investigational site’s role in RBM more than other early publications.
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The publication highlights basic rules for implementing RBM directed at the clinical sites themselves. These rules include prompt submission of data in order to aid in effective centralized monitoring, site personnel’s comprehension of the RBM approach and recognition of their responsibility to maintain accurate subject data, and established clinic procedures designed to ensure data accuracy.

Three main themes emerge as significant concerns for clinical sites in regards to RBM. First, due to the dynamic and variable nature of the RBM strategy and the lack of consensus as to what constitutes RBM, there is a gap in understanding between site and Sponsor/CRO in regards to the implications of applying the strategy. This naturally has led to misunderstandings and assumptions from both parties. Second, there is a concern regarding fair compensation for the change in services the site provides and the tasks which they are asked to perform. The third theme that emerges is that in practice, introducing RBM has challenged relationships between Sponsor/CRO and site for reasons that may include the misunderstandings afore mentioned as well as a change in the nature of, and often decrease in, contact.

**Recommendations**

Through a review of the results and recommendations from these recent sources, Sponsors and CROs can focus on RBM quality improvement efforts that address real-world site concerns. The following are key activities that, when undertaken, should lead to more successful RBM trials:

**Communicate regarding the RBM Strategy**

Misunderstanding between Sponsor/CRO and site should be no surprise given the variability in RBM’s utilization and implementation. As early as conversations about sites of interest and qualification visits, any potential for RBM should be communicated to site personnel, including the investigators, research coordinators, and research administrators. Be honest with sites from the beginning regarding whether or not they may be monitored 100% of the time, and that the nature and frequency of monitoring could vary throughout the trial given the dynamic nature of RBM. Ask site personnel if they have ever participated in a study that used a risk-based approach or remote monitoring. Seek to understand the extent of their experience, how the method has been presented to them in the past, and how that affects their view of alternative monitoring practices. If they feel they were “burned” in the past, address their concerns up-front. If they had good experiences in the past, ask them what worked best and
tailor those elements to the current study. Communicate the advantages of an RBM model from the site perspective, emphasizing the increased focus on high-risk areas in the interest of preventing errors that would have a significant impact on subject safety, the integrity of the trial, and regulatory compliance. Point out the greater flexibility and ability to redirect resources. It may be helpful to refer to regulatory guidances and reputable publications regarding RBM. Sponsor/CRO should work together to prepare statements to be used consistently with sites who have questions regarding the monitoring plan. Common questions sites may ask include: can sites choose to have on-site monitoring visits even if they do not meet the RBM thresholds, and what types of findings would trigger additional monitoring at my site?

Include RBM in site initiation discussions and training on RBM in conjunction with protocol training. The training should include an overview of the purpose and justification for the RBM approach, the risk factors identified in the risk assessment, and how periodic review of site metrics will help inform ongoing decisions about monitoring activities. A discussion around the site’s own internal processes should be included to ensure the site understands their own responsibilities and has the means to conduct alternative monitoring activities such as remote monitoring and use of electronic files.

**Rethink Compensation**

If emphasis has been primarily on a reduction in SDV, the clinical site may have the impression that RBM is only about saving the Sponsor money. If this is the case, it will be a challenge to get site buy-in for a new RBM strategy. Open communication and education on the core principles of RBM can help clarify the purposes of the strategy; however, direct focus on negotiating the site study budget in light of the monitoring plan seems to be what sites are asking for. A monitoring plan that involves fewer on-site visits and a subset of data monitored does not necessarily equate with less time required on the part of the research coordinator. The workload reduction realized in an RBM trial will ideally be manifested in lower query rate, protocol deviations, monitoring findings, and an overall increase in study quality. This should be emphasized with the site during budget negotiation. The following elements should also be discussed and taken into account when working with the site to determine a fair budget:

- If remote monitoring will replace a portion of on-site monitoring, which may involve additional administrative work such as copying, redacting, scanning, and uploading of source, who will be responsible for this activity at the site? Does the site have research assistants who can be responsible for this versus the primary research coordinator? If so, salary could be taken into account. For example, an on-site traditional visit may primarily involve multiple days-worth of a primary coordinator’s time, while an abbreviated, remote visit may involve a few hours of a research assistant’s time and a couple hours of the primary coordinator’s time.

- Consider the likely range of anticipated monitoring visits, both on-site and remote, that could be required in the study. An RBM study may have a wider range of possible visits due to the constant evaluation of risk, but that range may still be less than a traditional plan that involves a guaranteed number of visits with potential for additional “for cause” visits.

- In the case of an RBM plan that involves randomization of sites, with a subset of sites receiving minimal monitoring and a subset monitored significantly more, discuss how this will be accounted for in the budget. For example, if there is one budget template for all sites and randomization does not occur until after budget execution, how much extra resources will a site need to have 100% source data verified versus an un-randomized site that will only have informed consents verified?
Recommendations

• With less frequent monitoring, traditional payment terms tied to monitored data will need to be adjusted. Payment may need to be tied to data reviewed remotely rather than data fully monitored in order to ensure sites are receiving payments on a reasonable schedule.

Expect to seek creative solutions to budget negotiations that involve an RBM study. In preparation for discussions with sites, it may be helpful to create a budget template that assumes 100% on-site, traditional monitoring. Then, adjust elements that would change in the risk-based scenario, keeping in mind the nature of activities involved and the roles and salaries for site personnel responsible for each activity.

Invest in Relationships

The transparency shown in first contacts, RBM training, and flexible budget negotiations, will go a long way to lay down a solid foundation of trust between Sponsor/CRO and site. The same level of care should be taken throughout the life cycle of the study to maintain and strengthen the partnership. It is clear through the literature that sites have been frustrated and feel a reduction in quality communication with Sponsors/CROs in RBM trials. The nature of the risk-based approach, however, should actually lend itself to a closer relationship—signifying focus is shifted from a historically after-the-fact, correction approach to non-compliance, to a more preventative focus. Activities, such as centralized review of aggregate data throughout the study and timely remote data review, can be presented to sites as ways the Sponsor/CRO is working for the benefit of the study and the site to catch trends and errors early in order to prevent more long-term issues that will affect the site’s reputation.

The challenge though, with maintaining open communication with sites in a risk-based trial, is the reduction in required on-site, face-to-face visits. The main resource available to sites to address their questions and concerns shifts from the monitor out in the field, to potentially several internal personnel such as internal monitors, data reviewers, data management personnel, and site managers depending on the organizational structure of the Sponsor and/or CRO. Therefore, it is essential that roles be established internally and responsibilities clearly defined, so a consistent message is sent to the site regarding their questions, and a main contact is established who will be responsible for checking in with the site regularly. Listen to the site’s concerns regarding communication, and be creative in offering alternatives such as video conferencing, first patient walk-throughs over the phone, or additional on-site visits. The sites may need extra encouragement and prompts to reach out with questions when regular on-site visits are not planned. The focus afforded by RBM should be leveraged to aid in communication and cohesion that is the result of sharing a common cause.

Conclusion

The RBM approach is sophisticated and involves the orchestration of many different activities during the planning phase of a trial. It is easy for a Sponsor/CRO to lose sight of the perceptions and needs of the clinical sites. Utilizing resources provided by organizations such as ACRP and SCRS can help maintain a finger on the pulse of the ever-changing site experience. Currently, significant concerns for clinical research sites include misinterpretation and confusion regarding the meaning of RBM, fair compensation in an RBM trial, and relationship strains and lack of communication with Sponsor/CRO. By utilizing strategies such as early education on RBM, transparent and creative budgeting, and a deliberate approach to maintaining partnerships, the RBM trial has the potential to strengthen relationships and the quality of clinical trials.
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References


