WHITE PAPER

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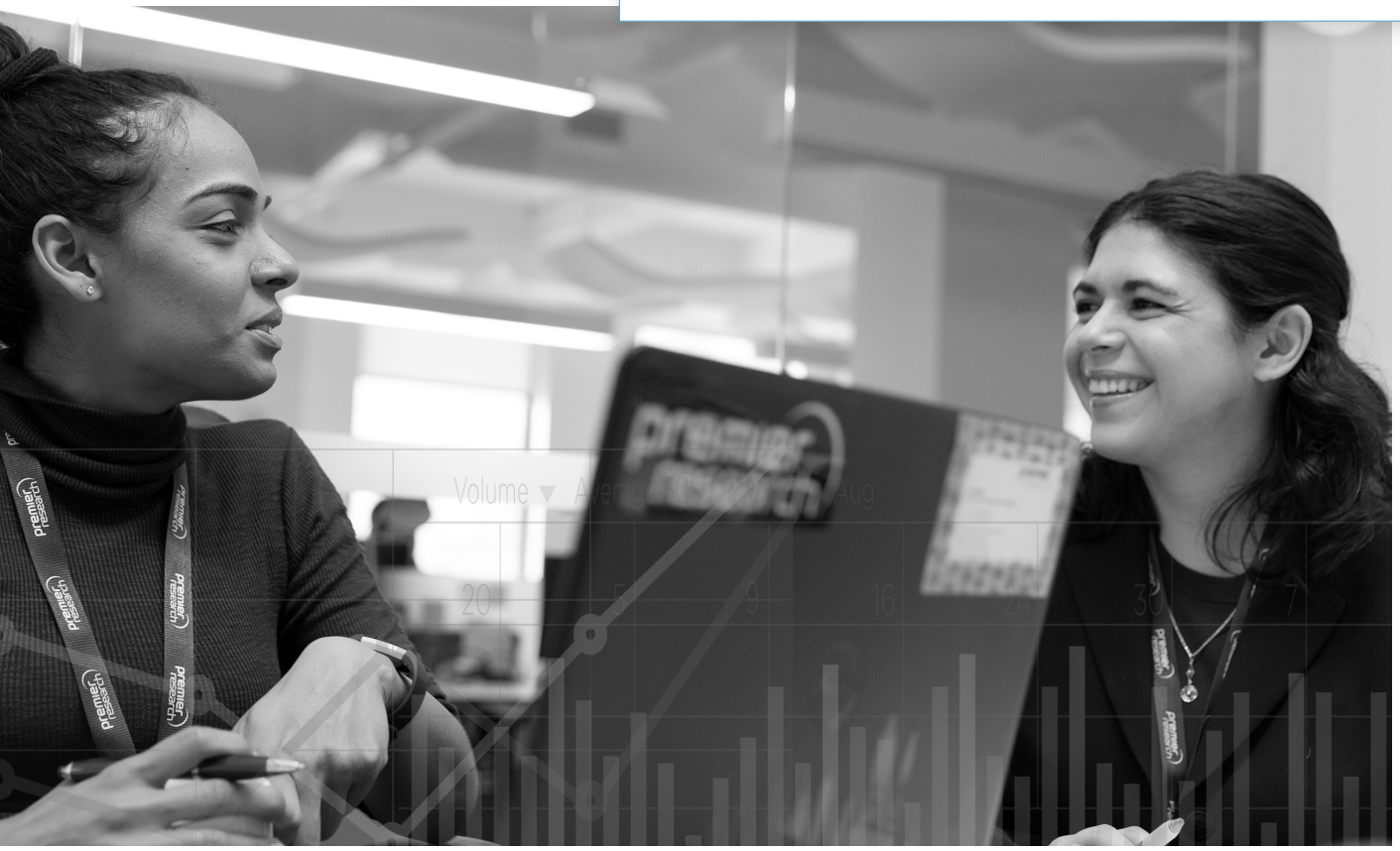
MEDICAL DEVICE

Planning for Quality in Medical Device Clinical Trials

ABSTRACT

Risk-based monitoring is a comprehensive approach to clinical trial monitoring that focuses on proactively identifying and addressing risks to patient safety and data quality. Effectively navigating the shift from traditional on-site monitoring to risk-based monitoring requires cross-functional collaboration and careful planning.

The recent revision of the ICH Guideline for Good Clinical Practice E6 (R2) from 2016 puts RBM back in the spotlight.



Introduction

For more than a decade, the concept of RBM has been discussed, implemented, and refined in the pharmaceutical and medical device worlds. While most large manufacturers in the medical device industry have incorporated RBM into their clinical trials, smaller medical device companies have been slower to embrace the concept.

The recent revision of the ICH Guideline for Good Clinical Practice E6 (R2) from 2016 puts RBM back in the spotlight. In addition, the upcoming new version of the ISO 14155 standard for medical device clinical investigations and Good Clinical Practice will emphasize that RBM is more relevant and necessary than ever.

In this white paper, we discuss RBM and explore how to effectively implement this monitoring approach into medical device clinical trials in a methodical and compliant manner.

Background on clinical trial costs in pharma

Currently, there are approximately 290,000 studies registered on ClinicalTrials.gov.[1] Study budgets increase as drug development advances:

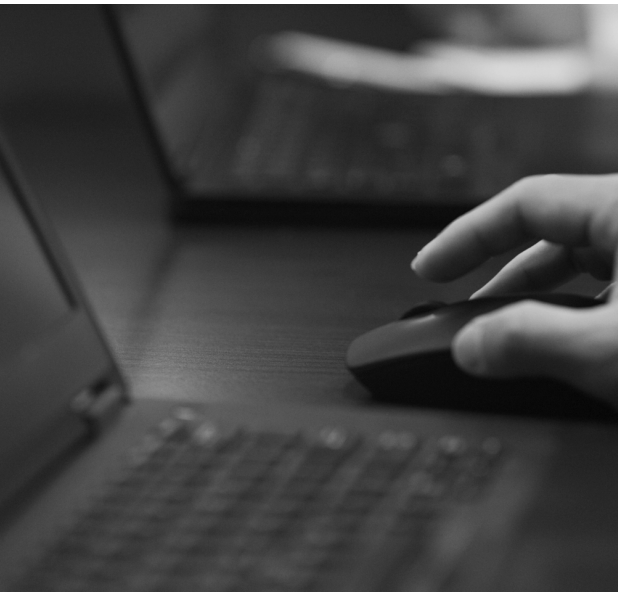
- **Phase I** – $1.4-6 million
- **Phase II** – $7-19 million
- **Phase III** – $11-52 million

Looking more closely at a breakdown of study budgets by cost component and phase, it is clear that site monitoring and source data verification (SDV) are key drivers of clinical trial costs, accounting for 20-25 percent of total budget (see Figure 1). It can be assumed that a similar percentage of costs is applicable for medical device trials.

Figure 1. Clinical trial costs by cost component and phase[2]

Cost component	Phase I		Phase II		Phase III	
	US$	% of subtotal	US$	% of subtotal	US$	% of subtotal
Per-patient costs						
Patient recruitment costs	US$37,050 (US$21,666)	1.74	US$161,140 (US$102,066)	2.12	US$308,672 (US$174,702)	2.71
Patient retention costs	US$6,145 (US$4,745)	0.29	US$15,439 (US$6,970)	0.20	US$24,727 (US$15,868)	0.22
Registered nurse and clinical research associate costs	US$178,237 (US$90,473)	8.36	US$441,053 (US$140,390)	5.80	US$939,540 (US$614,943)	8.25
Physician costs	US$109,681 (US$57,626)	5.15	US$381,968 (US$117,217)	5.03	US$805,508 (US$499,426)	7.08
Clinical procedure costs	US$475,667 (US$371,586)	22.32	US$1,476,368 (US$633,448)	19.43	US$2,252,208 (US$1,033,618)	19.79
Central laboratory costs	US$252,163 (US$203,342)	11.83	US$804,821 (US$313,577)	10.59	US$849,180 (US$600,134)	7.46
Per-site costs						
Site recruitment costs	US$51,904 (US$32,814)	2.44	US$233,729 (US$83,799)	3.08	US$395,182 (US$195,983)	3.47
Site retention costs	US$193,615 (US$79,974)	9.09	US$1,127,005 (US$544,068)	14.83	US$1,305,361 (US$1,382,296)	11.47
Administrative staff costs	US$237,869 (US$128,547)	11.16	US$1,347,390 (US$427,859)	17.73	US$2,321,628 (US$1,910,047)	20.40
Site monitoring costs	US$198,896 (US$128,142)	9.33	US$1,083,186 (US$392,798)	14.25	US$1,624,874 (US$717,034)	14.28
Per-study costs						
Data management costs	US$50,331 (US$8,467)	2.36	US$59,934 (US$21,060)	0.79	US$39,047 (US$19,416)	0.34
Cost per IRB approvals	US$11,962 (US$6,305)	0.56	US$60,188 (US$16,092)	0.79	US$114,118 (US$46,404)	1.00
Cost of IRB amendments	US$1,094 (US$255)	0.05	US$1,698 (US$447)	0.02	US$1,919 (US$277)	0.02
Source data verification costs	US$326,437 (US$65,659)	15.32	US$406,038 (US$80,573)	5.34	US$400,173 (US$66,429)	3.52
Subtotal (in US$ million)	US$2.13 (US$0.86)	100	US$7.60 (US$1.46)	100	US$11.38 (US$4.93)	100
Site overhead	US$528,685 (US$235,862)	n/a	US$1,741,811 (US$302,049)	n/a	US$2,541,313 (US$1,091,082)	n/a
All other costs	US$1,139,887 (US$468,077)	n/a	US$4,003,615 (US$752,108)	n/a	US$5,967,193 (US$2,577,692)	n/a
Total (in US$ million)	US$3.80 (US$1.56)	n/a	US$13.35 (US$2.51)	n/a	US$19.89 (US$8.59)	n/a

Adapted from Sertkaya A, et al. Key cost drivers of pharmaceutical clinical trials in the United States. Clin Trials 2016;13(2):117-126.



The trend toward risk-based monitoring

RBM is an indicator of quality in a clinical trial and allows for a more in-depth assessment of site data, without requiring additional time on site. In recent years, both regulatory and industry guidelines have been promoting a risk-based approach to clinical trial monitoring.

FDA: Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring[3]

A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers Guidance for Industry[4]

These guidance documents assist sponsors in developing risk-based monitoring strategies that enhance human subject protection and clinical trial data quality by focusing oversight on the most important aspects of clinical trial conduct and reporting. The FDA recommends a quality risk management approach and emphasizes that quality is an overarching objective that must be built into the clinical trial enterprise.

The RBM approach was already implemented for pharmaceutical clinical trials by publishing the revised ICH GCP E6 (R2) guideline:

ICH: ICH Good Clinical Practice (GCP) E6 (R2) Guideline[5]

The overall objective of this guideline is to increase clinical trial quality and efficiency while continuing to ensure both patient safety and data quality. ICH E6 (R2) requires sponsors of pharmaceutical trials and contract research organizations (CROs) to develop a systematic risk-based approach and to document the rationale for the strategy. This must be done through a risk assessment looking at critical processes and risk identification, evaluation, control, communication, and reporting.

While the ICH E6 (R2) guideline is not fully applicable to medical device clinical trials, device manufacturers can expect the revised ISO 14155 standard to include more robust, comprehensive risk management requirements across all phases of the medical device clinical investigation process. Therefore, implementing solid RBM processes should be part of every device company's agenda.

In 2013, the European Medicines Agency (EMA) published a reflection paper on RBM:

EMA: Reflection paper on risk based quality management in clinical trials[6]

This paper encourages the development of a more systematic, prioritized, risk-based approach to quality management of clinical trials. The basic premise of risk-based quality management is to identify risks on a continuous basis throughout the design, conduct, and reporting of clinical trials and to build quality risk management into the clinical trial protocol and other trial-related documents.

An approach to risk-based quality management

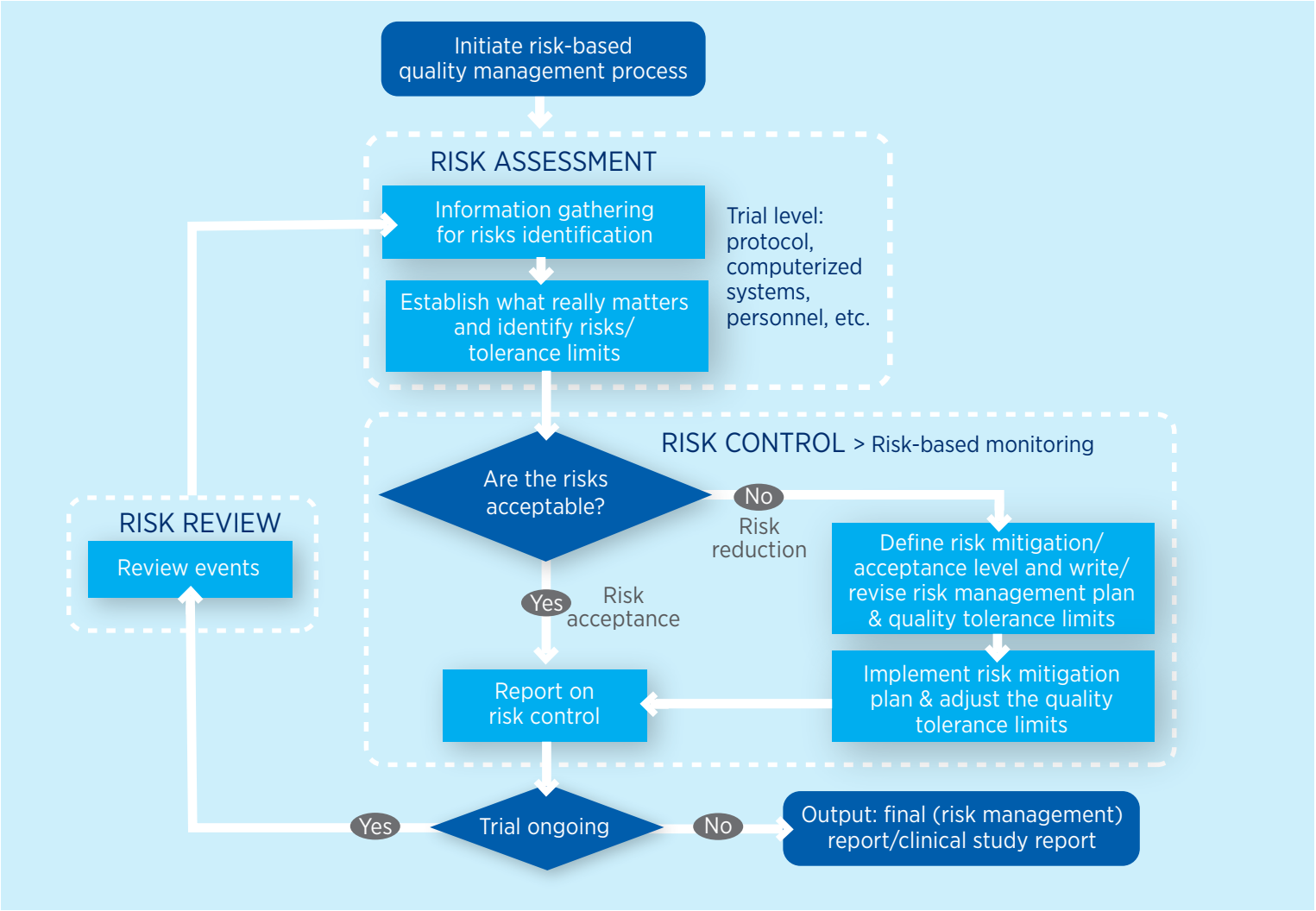
In this reflection paper on risk-based quality management in clinical trials, the EMA provides an illustration of how this process could to applied to clinical trials (see Figure 2) by implementing the following three steps:[6]

- **Risk Assessment**. The goal of this step is to gather information on the single clinical trial elements to identify risks and to develop tolerance limits
- **Risk Control**. The aim of this part of the process is to define risk mitigation and acceptance levels and to develop — and implement — a risk management plan, including quality tolerance limits, which may be adjusted as the clinical trial unfolds
- **Risk Review.** This step involves ongoing reassessment of risks through review of new information that emerges during clinical trial conduct

Manufacturers should keep in mind that all quality management processes are dynamic and are constantly adapted as additional information becomes available.

From the information provided so far, it can be concluded that RBM is not only embraced but is now expected by most regulators.

Figure 2. Depiction of a risk-based quality management system for clinical trials[6]



Adapted from European Medicines Agency. Reflection paper on risk based quality management in clinical trials.
Available at https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-risk-based-quality-management-clinical-trials_en.pdf

In a traditional on-site monitoring approach, clinical research associates (CRAs) visit sites at a given frequency and perform 100 percent SDV with the goal of ensuring that all clinical trial data is accurately transcribed to the case report forms (CRFs) in the clinical trial database.

Comprehensive risk-based monitoring

RBM is a component of the risk-based quality management system described previously, and it falls under the step of risk control as a mitigation strategy. The concept of a comprehensive RBM approach is comprised of four pillars:

1. **Centralized monitoring**. Provides remote evaluation of aggregated clinical trial data based on a statistical concept, where data is analyzed to assess key risk indicators, as well as the need for — and timing of — mitigation of adverse outcomes. Review is performed on an ongoing basis of the real-time clinical trial data sets.
2. **Reduced monitoring/Source Data Verification (SDV)**. Involves fewer on-site visits and less than 100 percent SDV of patient data, depending on the protocol or individual site risk. With reduced monitoring, prioritization of data determines the SDV level (e.g., 100 percent SDV for critical endpoint data and 20 percent SDV for less-critical data).
3. **Targeted/triggered monitoring**. Ties to centralized monitoring and uses pre-defined data entry situations or issues to trigger on-site visits (e.g., low rate of serious adverse event reporting at one site compared to other sites).
4. **Remote monitoring**. Utilizes an approach whereby activities that are traditionally considered to be covered on-site are conducted remotely instead.

Comparing traditional on-site monitoring to risk-based monitoring

On-site monitoring

In the past, with on-site monitoring, all sites and patient data are treated equally and the objective was 100 percent error-free data. In this traditional on-site monitoring approach, clinical research associates (CRAs) visit sites at a given frequency and perform 100 percent SDV with the goal of ensuring that all clinical trial data is accurately transcribed to the case report forms (CRF) in the clinical trial database. Interestingly, research has shown that a large random transcription error with a frequency of up to five percent in the CRF does not significantly influence the outcome of a trial.[7]

Of note, researchers have found that the time spent on SDV accounts for between 46 and 75 percent of the monitoring visit, leaving only little time for other tasks such as reviewing clinical trial processes on-site, discussing with or retraining of the trial team, and maintaining the investigator site file.[8,9] According to a 2014 publication, less than four percent of CRF data required correction and only one-third of that data was identified by SDV. The study also found that approximately 50 percent of site visits were focused on SDV activities, contributing significantly to cost.[10]

To a certain extent, being on-site and focusing mainly on SDV results is a retrospective approach of fixing things which have already gone wrong. Instead, a more proactive approach would be to spend more time with site staff discussing trial matters and processes as this provides more opportunity to prevent potential non-compliance.

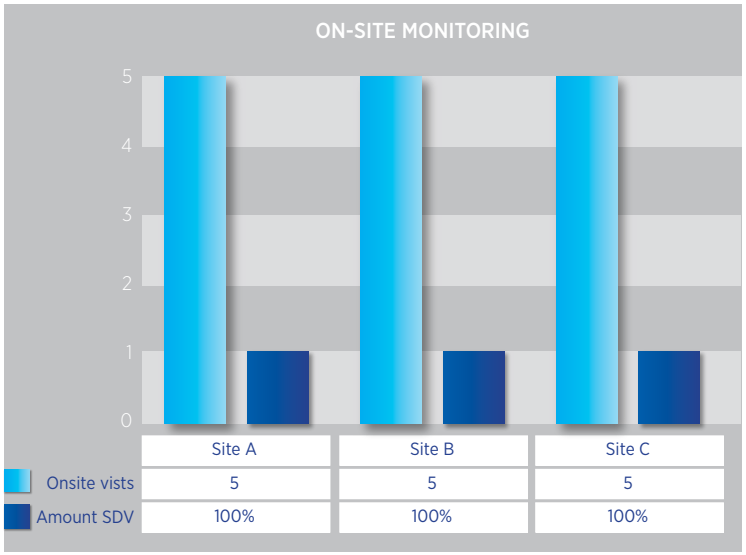
Risk-based monitoring

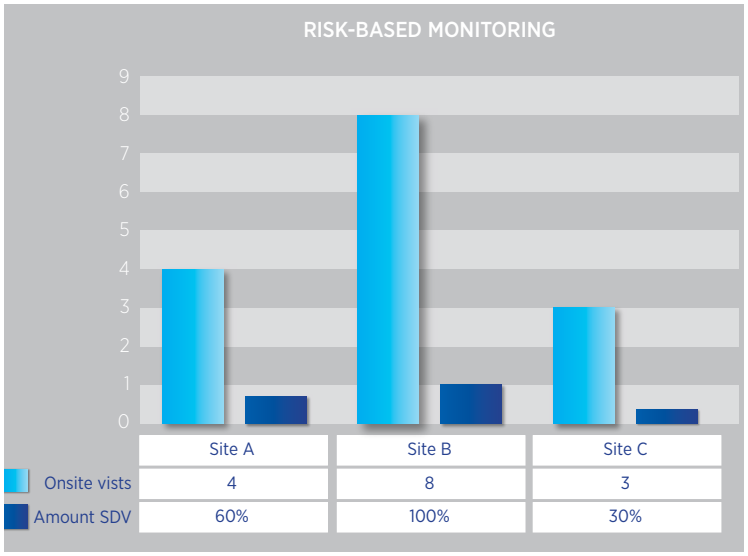
To implement meaningful RBM in a clinical trial, up-front thinking is of the utmost importance. The trial should be built on "quality by design"; protocols should be developed carefully while determining and assessing risks on all trial levels and asking, "What are my critical data and processes?" and how potential risk may affect those.

Once the critical data and processes are defined, the main effort of the quality control measurement will be to evaluate these, meaning continuously looking at the "risky parts" of the trial conduct. Compared to traditional on-site visits where all sites and data are treated the same way, RBM handles site and patient data according to risk with the aim of collecting data that is fit for purpose. In this example, sites with a high number of protocol deviation will be visited more frequently by a CRA than sites which are in compliance. It is anticipated that wider implementation of RBM will have a number of benefits:

- **Reducing costs**, while still ensuring patient protection and data validity. In fact, research suggests that risk-based monitoring could potentially lower clinical trial costs by 15-20 percent.[8]
- **Enhancing safety and quality**, using comprehensive RBM technology solutions that track trend information in real time and make actionable data readily available to the Central Monitor so corrective action can be taken earlier.
- **Improving timelines**, as data is reviewed on an ongoing basis and in real time with corrective actions following, reducing the time needed for trial database cleaning at the end of the trial.
- **Facilitating regulatory compliance**, as a robust RBM approach fulfills the expectations of the FDA, EMA, ICH E6 (R2), and the revision of ISO 14155.

Figure 3. Traditional on-site monitoring vs. RBM





Implementing risk-based monitoring in a clinical trial

Implementation of RBM in a clinical trial requires careful, proactive planning.

Clinical trial planning phase

- **Perform risk assessment and categorization**. Cross-functional collaboration is required to identify, assess, and categorize risks at both the system level and the clinical trial level
- **Define critical data and processes**. This involves defining the data and processes that are critical to ensuring patient safety and data quality (e.g., critical data is usually associated with the trial endpoints)
- **Develop a trial-specific quality and risk plan**. This plan should include risk indicators, system tools, and processes for implementation
- **Create monitoring plans**. This plan should clearly define the monitoring strategies, when to go on-site, and what the off-site activities will be

Active clinical trial phase

During the active trial phase, central monitoring will be performed on an ongoing basis, where aggregated trial and operational data are reviewed and assessed according to the defined Key Risk Indicators (KRI) and their associated thresholds. In case thresholds are exceeded, the central monitor will initiate the respective action, which was already defined in the Quality and Risk plan. Actions could include targeted on-site monitoring activities or retraining of site staff via phone. Otherwise, routine on-site visits will be performed as defined in the monitoring plan.

When implementing RBM, however, it needs to be understood that the risk review is an adaptive process and thresholds may need to be revisited and refined when more trial data becomes available. The regular review of data during such risk review meetings will ensure that additional adjustments are made to the trial plans and the documented processes when necessary, therefore being a true adaptive approach which is following the PDCA cycle: Plan-Do-Check-Act.

Using a central monitoring system

Central monitoring systems are data warehouses which pull data from available clinical databases, such as the electronic CRF (eCRF), clinical trial management system (CTMS), or central lab. These systems allow central monitors to visualize and analyze data for signal detection and trend analysis in a “storytelling manner” and to initiate action, if needed.

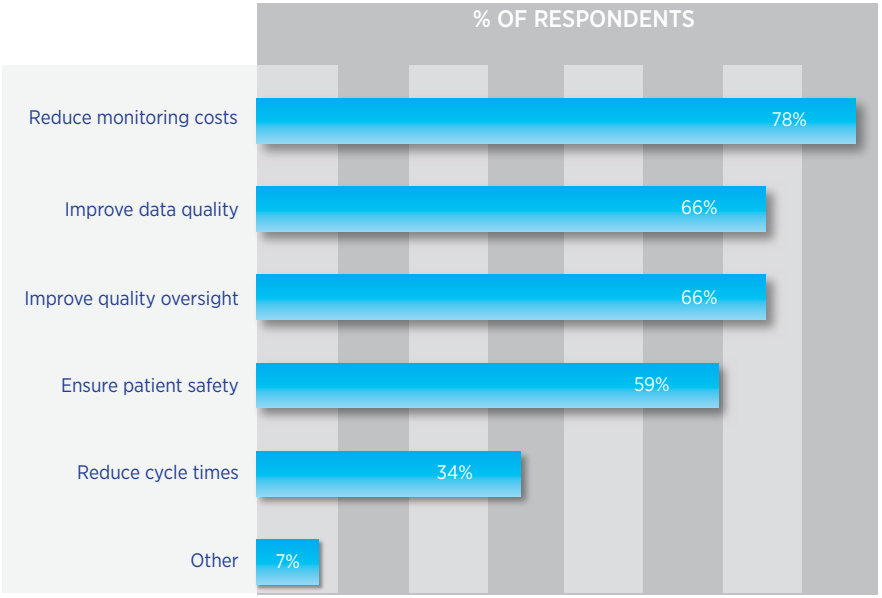
A system with an integrated, customizable risk assessment categorization tool (RACT) can be used to implement RBM, beginning in the protocol planning phase and continuing throughout clinical trial conduct. Sponsors can tie risks identified during the risk assessment to data points collected during the clinical trial and set thresholds on these data points. If these data points begin to deviate toward an unacceptable range, an alert can be sent to the central monitor, who investigates the root cause and escalates to the appropriate team member before the issue becomes critical.

With the right software, monitors can now also drill down to the site level to visualize and analyze deviations or queries or even to the patient-level data. Central monitors can review abnormal data patterns, perform signal detection, do trend analysis, and identify data outliers and inliers to an extent which is not possible for an on-site monitor with the isolated view of “just” the sites’ data. This central review of real-time aggregated data can improve the trial data quality immensely.

The future of risk-based monitoring in medical device trials

Currently, while RBM is seen more frequently in pharmaceutical clinical trials, overall adoption remains low with implementation in less than 25 percent of studies.[11] For medical devices, it is mainly the large manufacturers who have begun to utilize RBM in their clinical trials. According to a Metric Champion Consortium survey, the top motivations for adopting RBM are reducing monitoring costs, improving data quality, and improving quality oversight (see Figure 4).[12]

Figure 4. Key reasons for adopting risk-based monitoring (n=41)[13]



The reduction of monitoring costs and improvement of data quality can be seen in one prospective randomized study where more than 200 trial sites from 11 academic trials were randomized to on-site monitoring or RBM method. Post-trial audits were performed to determine the frequency of major GCP findings at patient level. RBM was found to be non-inferior to extensive on-site monitoring in terms of data quality whereas costs for monitoring were reduced by 50 percent.[14]

Despite the relatively low adoption rate, regulators are calling for assurances of patient safety and data quality by implementation of RBM. Additionally, with the passage of the Medical Device Regulation (MDR) in the EU, it is anticipated that an increasing number of medical device clinical trials will need to be conducted for new or continuing market access. In this regulatory environment, it is important for device manufacturers to consider implementing an RBM approach for conducting cost-efficient, high-quality clinical trials that generate the data needed for obtaining or maintaining a CE mark.

Conclusion

With its emphasis on identifying and addressing the most important risks to patient safety and data quality, RBM provides a data-driven, cost-effective approach to clinical trial monitoring. As device manufacturers are increasingly required to conduct clinical trials to achieve market approval and access, implementation of a comprehensive RBM approach can help improve the safety, quality, and efficiency of the development process while also controlling costs.

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Kirsten Welz | Associate Project Director – Medical Device & Diagnostics

With a degree in biology, Kirsten started her career in clinical research as a clinical research associate progressing to a clinical trial leader then clinical project manager. With this broad experience in the field of pharmaceutical and medical device studies as well as deep insight into different indications and national regulations, she worked for several years as an independent consultant, covering positions like CRA, clinical project manager, GCP-trainer for study sites and CRAs, quality manager, and other supportive functions for inspection preparations.

At NAMSA, she was fully dedicated to pre- and post-market medical device studies mainly in the U.S., Europe, and Asia Pacific. Next to her project management role, she was also involved in medical writing, site auditing, and regulatory activities and acted as trainer for sites and CRO staff. Kirsten is currently an associate project director at Premier Research, focusing on medical device studies. Her main therapeutic experience is in cardiology with special focus on interventional cardiology to treat coronary artery diseases, mitral valve insufficiencies, and atrial fibrillations.

Vicki Gashwiler | Executive Director, Program Strategy – Medical Device & Diagnostics

Vicki Gashwiler joined Premier Research in 2019 as the executive director of strategic development in the Medical Device & Diagnostics group. She brings over 13 years of experience in the medical device industry, both on the sponsor and CRO sides. Vicki began her career as a registered nurse working on cardiac, critical care, and out-patient orthopedic surgical units. She started her industry career at Abbott Vascular and had the opportunity to support global clinical trials spanning Europe, Canada, Latin America, Australia, the U.S., and Asia-Pacific which provided her an extensive understanding of complex trial execution on a global scale, diverse team management, and global regulatory processes and timelines.

In 2014, Vicki joined Novella Clinical filling roles of increasing responsibility including senior project manager, program director, associate director, and director of Strategic Development & Market Access. Vicki brings high-level understanding of market development and trends as well as a deep therapeutic knowledge of many disease processes and the clinical trials to intervene upon them.

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