



# Case Studies in Successful Implementation of Effective Risk-Based Monitoring in Medical Device Companies

Medical Device Innovation Consortium (MDIC)  
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## I. Introduction

Medical device clinical study oversight is critical to both protecting patient welfare and ensuring high-quality study conduct. FDA requires sponsors of clinical studies provide this oversight, commonly referred to as Monitoring, to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality of the clinical trial data submitted to FDA.<sup>1</sup> Effective monitoring of clinical study conduct has been a focal point for many years within the medical product (pharmaceutical, device, and diagnostic) ecosystem. In the United States, as well as in other jurisdictions, the goals of monitoring have been clear: provide assurance that the clinical trial is being conducted according to the protocol so that complete and proper data are collected and, most of all, provide assurance that patients are being appropriately protected. Yet, identification of best practices to accomplish these goals has not always been clear.

Today, the principles of risk-based clinical trial monitoring have not been widely adopted in the medical device clinical trial ecosystem, despite FDA issuance of the Risk-Based Monitoring (RBM) [Guidance](#) (2013) to support the use of this approach. In part, this adoption shortfall has been attributed to a perception by sponsors that FDA prefers monitoring obligations be met through frequent on-site monitoring visits and 100% Source Data Verification (SDV).<sup>1</sup> Given this apparent dichotomy, there exist opportunities for more RBM implementation research and reporting from device sponsors, and for the creation of RBM implementation tools to assist sponsors and investigators. As FDA, sponsors, and other stakeholders collaborate to ensure that U.S. patients have access to high-quality, safe, and effective medical devices, the use of commercial technological innovations (such as electronic data capture and electronic medical records), combined with structural evidence development innovations (such as a National Evaluation System for health Technology - NEST), present opportunities to facilitate innovation and efficacy in monitoring.

## II. RBM Organizational Change Management: A Case Study

Risk-Based Monitoring, while relatively new to the clinical trial space, is not a novel idea. It is based on the principles of Project Risk Management, one of the ten generally recognized knowledge areas of project management,<sup>2</sup> and Quality by Design, a concept first outlined by quality expert Joseph M. Juran<sup>3</sup> in the early 1990s. Project risk is defined by the Project Management Institute (PMI) as “an uncertain event or condition that, if occurs, has a positive or negative effect on a project’s objectives.”<sup>2</sup> As applied to clinical trials, this involves a more efficient approach by the sponsor to continually assess, manage, and mitigate the untoward “events or conditions” that could occur in a clinical study. This approach is intuitively attractive in a complex ecosystem driven by both budget constraints and continuous adaption to geographically distinct regulations under jurisdictions by differing agencies. Given these ecosystem dynamics, RBM presents an opportunity to optimize resources while maintaining adequate sponsor oversight to ensure trial quality and patient protections. The (a) recent work by Transclerate Biopharma<sup>4</sup> to outline a practical methodology for using RBM, as well as (b) endorsement by governing bodies such as the FDA<sup>1</sup> and the European Medical Agency<sup>5</sup> have been pivotal towards facilitating pharmaceutical and medical device companies to target this space for strategic process improvement in clinical trial execution.

## Implementation Principles

The motivation for implementing RBM to the sponsor providing this case study was driven primarily by Quality—targeting efficient yet effective sponsor oversight. In keeping with the Plan-Do-Check-Act cycle, the sponsor pursued the following approach:

1. Risk Assessment and Risk Categorization (Planning Phase): Identification and categorization of the likelihood, impact, and detectability of an untoward event or occurrence.
2. Central Monitoring: Process definition for continual production and review of data both at a site and at a study level (risk indicators, system tools, and reports). In order to visualize the full picture and create consistency, cross-functional expertise was incorporated into the review of periodic data through the incorporation of a central team.
3. Response/Action: A process to ensure that any issues noted from these periodic reviews were appropriately dealt with based on severity, owners assigned, and tracked to closure.
4. Periodic Review of Indicators and Risks: The workflow itself was created with flexibility to handle potential changes throughout the course of the multi-year study.
5. Audit Trail: This entire process was engineered with traceability and auditability in mind, such that adequate documentation of the entire process would be ready at any given time.

## Human Element Management

As a large medical device manufacturer executing multiple trials, with medium- to large-sized teams acclimated to operating under “traditional” processes and functional silos, transformation to a “risk-based” approach represented just as much of a challenge as it did an opportunity. This was mainly attributed to the mindset change required from team members. In a risk-averse industry (as evidenced by 100% SDV and on-site monitoring), such changes can appear dramatic. An important learning is that individuals without risk management experience may initially perceive RBM as introducing additional risk into the system. In this case example, many functional experts and team management were not well-versed in the principles of risk management. Therefore, a sustained effort was required to convert them to accepting RBM. In addition, shifting to the “risk-based” thought process suggests potential changes to roles within the clinical operations team. Valid concerns around “how will it affect my job?” along with doubts around “will I miss something if I do it differently?” had to be addressed early on to position the team for success. This paradigm shift was a significant exercise in change management, equal to the efforts on the technical and process fronts. Assigning dedicated resource time across all functions, and a project manager to facilitate detailing and rolling out the RBM process, was required to facilitate the effort.

In the learning phase, training and education came from sources of information including publications, conferences, and external experts. Additionally, multiple discussions with RBM systems vendors to assess availability of ready-made tools ensued. This phase also resulted in development of knowledge around future functional roles and potential ways to implement the model with least disruption within the organization. Building this internal expertise, through early and continued contact with external experts involved in successful RBM rollouts, helped significantly with both (a) planning for the technical and procedural aspects of the project, and (b) avoiding common pitfalls.

Human element needs were systematically addressed along with the change in mindset, starting at the top level. RBM conversion was definitely not a “plug-and-play” process. It took substantial time to educate staff, build the required tools, develop associated

procedures, and define indicators, thresholds, and escalation paths. Buy-in from senior leadership was required early on, and in sustained fashion, as a critical support, both in terms of funding commitment as well as timeline support. Senior leadership acceptance of a primary focus on Quality, and not on efficiency, was another critical factor to the RBM initiative's success. This acceptance helped build overall confidence in the processes and teams managed. As the project progressed through its Strategy, Design, and Implementation phases, engagement with every layer and function within the Clinical organization ensured alignment and vision investment. Ownership of the program's success was created by involving stakeholders spanning grassroots to management early in the sponsor's development of the RBM model. This involvement was supported with guidance and facilitation of external and internal RBM experts. Measures of success and check-points were incorporated at various intervals to assess the pulse of the project through development and implementation.

### **Capability Assessment and Vendor Identification**

External or internal systems supporting the successful execution of this program were addressed in parallel. Multiple small and large vendors offering "plug-and-play" solutions were identified. Internal investigations identified some existing system tools utilized by other departments within the organization as viable solutions the Clinical team could leverage for RBM. While considering both external and internal options, it was identified that the costs and complexities associated with system tools and integrations are not trivial and required discussion with the functional experts and right stakeholders within the organization.

### **Workflow Management**

The RBM workflow itself was not too complex to develop, but there were several details that were challenging to work through from a "where is this data point coming from?" perspective. Organizations with both change-ready teams (possibly due to Quality concerns under the current model or actively looking for immediate process efficiency) and adequate resources can work through these details over multiple face-to-face process review and continuous improvement sessions in a short period. If change acceptance or current workload is a concern, as it was for this sponsor, the project can be managed as an ongoing project over several months through weekly video and phone conferences.

When developing the rollout plan, one option is to switch over all studies to the new RBM model at once. This forces the organization to adapt and learn quickly, at the risk of added stress at the onset of the change. Depending on an organization's number and criticality of studies, the risk of the RBM model's early failure may be significant. This sponsor opted for a more conservative option by testing the model on a few pilot studies in order to learn through the RBM process. This refined the RBM process prior to full-scale rollout across all studies, increased organizational expertise, harmonized model adaption with learnings, and accommodated time to orchestrate the mindset changes. Of note from this sponsor, the pilot approach did create process risk of individuals working on both RBM and non-RBM studies, thus having to follow different processes for each.

### **III. RBM Operationalization: A Case Study**

The sponsor providing this second case study also acknowledged that the departure from 100% source data verification caused many veteran Study and Monitoring Managers to cautiously assess the impact RBM would have on the quality and validity of clinical study data. When considering application of a RBM strategy to a study, the foremost considerations in this sponsor's decision-making process were: Data Quality and Data

Validity. Upon conducting a review of ongoing Investigational Device Exemption (IDE), Post Approval, and Post Market studies, this sponsor found itself in a position to employ RBM models across multiple regulatory scenarios.

**Risk Assessment: RBM Applications**

Maintaining confidence in how RBM was being utilized was critical to the organization. Applying a formal Risk Assessment process was a useful operationalization step. Applying structured Risk Assessment to both new and ongoing studies fostered stakeholder confidence that projects most likely to benefit from RBM strategies were being correctly identified. This assessment (Table 1) included careful consideration of:

- Regulatory Status (for the medical device being studied): The most common types of medical device studies include Investigational Device Exemption (IDE), Condition of Approval Post Approval Study (COA), and Post Market Study (PMS).
- Medical Device Risk: Product and/or procedure
- Therapeutic Indication: Patient population
- Study Operations: Study (endpoints and data collection), site experience/personnel, and geographies in which the study is being conducted.

Each of these criteria was reviewed to determine a “risk profile.” For those studies with an overall low- to medium-risk profile, a RBM approach was employed. This model was considered on a case-by-case basis in cooperation with each study team.

Table 1: Risk Assessments for Risk-Based Monitoring Applications (Example)

	Regulatory Risk	Study Risk	Site Risk	Geographic Risk	Planned Data Utility	RBM Determination
	<ul style="list-style-type: none"> <li>• IDE = High</li> <li>• COA = Medium</li> <li>• PMS = Low</li> </ul>	L/M/H	L/M/H	L/M/H	For Other Submissions	Y/N
Study A	High	High	Low	Low	Yes	No
Study B	Medium	Low	Low	Low	No	Yes
Study C	Low	Low	Medium	Medium	No	Yes

**Opportunity Identification: RBM Return on Investment (ROI)**

Organizational adoption of a Risk-Based Monitoring model was critical to RBM’s success within the organization. Faced with an increased volume of regulated studies, larger sample size requirements, and an increased quantity of study sites, RBM facilitated the following ROI opportunities:

- Allowed the sponsor to ensure data quality in a more comprehensive manner.
- Facilitated conversations with stakeholders (study management, biostatistics, data management, and field support) resulting in focus and oversight on those data points critical to demonstrating a given study’s success.

- Evolution of study-specific Monitoring Plan detail describing data point (a) scope, and (b) specificity for studies adopting a RBM approach. These plans ensured the study team and monitors were provided clear focus for on-site monitoring requirements.
- Where data quality or site concerns were observed, the Monitoring Plan was provisioned for escalation, as warranted.

### **RBM Operationalization: Systematic Identification**

The sponsor's initial monitoring approach focused on identifying criteria (a) impacting a study's scientific validity, and (b) supporting a study's endpoints and objectives. Those criteria were next used to anticipate monitoring frequency and type/methods. Using a RBM pilot phase, prior to the benefit of RBM software, Clinical leaders partnered with Biostatistics to develop spreadsheets calculating multiple site risk criteria including: Enrollment, Adverse Events, Protocol Deviations, and Withdrawal Rates. These calculations resulted in each site being assigned a Key Risk Indicator (KRI) value. Review of a given site's KRI values in correlation to other study sites helped operationalize identification of those sites likely to benefit from additional on-site monitoring.

### **Outcome and Evolution**

As RBM methodology proved successful, the approach was expanded across the organization. A RBM Application platform was developed to support monitoring in a more automated and consistent manner. As the organization matured in its adoption of RBM, the monitoring approach evolved to include hybrid models such as:

- Monitoring a percentage of sites
- Monitoring a percentage of subjects at each site
- Monitoring pre-specified data points
- Monitoring certain subjects at each site according to total enrollment (e.g., first three subjects and every third subject after)
- Monitoring only when requested by the Study Team

As industry matures its utilization of RBM methods, the tools and data analytics guiding monitoring approaches mature as well.

## **IV. RBM Tool Development and Optimization: A Case Study**

As justifications for RBM became more widely adopted within the clinical study ecosystem, supported by FDA's publication of the final RBM Guidance in 2013, sponsors gained confidence in more fully exploring RBM strategies. This third case study describes the RBM tool development and optimizations that evolved following one sponsor's RBM integration journey. Similar to the previously described initial approaches, this sponsor recognized the need to raise organizational awareness and gain buy-in from Senior Management. During introductory meetings, across many geographies and functional groups, questions surrounding RBM's value, and specifically around cost savings, were raised. Consistent communications across the organization reinforced that implementing a risk-based clinical study approach is primarily to increase the quality of the trials and to ensure safety and well-being of subjects; cost savings were anticipated as a desirable side effect resulting from timely risk identification, mitigation, and preventative actions, all of which were expected to increase overall study quality.

### **Tool Development and Operationalization: Case Study Background**

The first meeting to discuss conducting a study, "Study D," under an RBM approach took place in November 2012. The study identified was a FDA-required Post Approval Study

(PAS), enrolling up to 26 sites and 124 subjects. Support for the decision to utilize a risk-based approach included experienced investigational sites and Principal Investigators (PIs) who had participated in the PAS study product's IDE trial, with study protocols of nearly identical procedures.

The risk-based strategy in the first version of the clinical monitoring plan (CMP) for Study D consisted of Centralized and Remote monitoring. While currently both are integrated into the sponsor's RBM approach, their initial RBM strategy was lacking in several core components of a true RBM strategy: namely, Risk Identification, KRIs, and KRI risk thresholds. Additionally, critical data were not specific in the Source Document Verification (SDV) plan, and interim visit frequency was arbitrarily set at a minimum of every 12 months. For Informed Consent Form (ICF) documentation, the SDV plan required 100% ICF review, although the strategy did allow for the utilization of technology to review ICFs (i.e., WebEx, FaceTime). The subsequent CMP accounted for these components resulting in a more robust and detailed RBM strategy which included site/study risks, KRIs, thresholds, and targeted SDV for critical data.

### **Tool Development**

An initiative was put forth to create more robust RBM tools, including: improved reporting, site risk assessment, and standardized formatting applicable to most studies. A RBM Core Team worked over the course of 6 months to:

- Create the tools
- Identify a pilot study (Study S)
- Train the pilot study team, and
- Execute the strategy

The study identified to pilot the improved RBM approach was an evaluation of a surgical procedure; no investigational devices were used.

### **RBM Tool Development I: Site Risk Assessment**

The RBM Core Team began with creation of the Site Risk Assessment tool (Table 2). The objective of this tool was to identify, before enrollment, those study sites that may carry a greater risk in terms of compliance, enrollment, and performance. To maintain broad study applicability, the criteria against which the sites were evaluated were general enough so that studies in all phases can evaluate sites against them. Flexibility was important to allow the study teams to add study-specific criteria that they found critical to successful oversight.

### **RBM Tool Optimization I: Site Risk Level**

One key learning from the Pilot Study included weighting of the Site Risk Assessment criteria in order to place more importance on those criteria most important to any individual study. The output of this evaluation was a Site Risk Level score: Low, Moderate, or High. This Site Risk Level (Table 2) was further leveraged as an input into the Trigger Report (described in the next section). A site's risk level is a modifier to the overall Site Risk Assessment. For example, if two sites had exactly the same KRI data, but one site was designated a Low risk and the other as a Moderate risk, the Moderate risk site would first cross the threshold for assessment of additional monitoring. Thus, Site Risk Level as a modifier to the Site Risk Assessment scores better categorizes an individual site's risk profile.

Table 2: Site Risk Assessment Tool (Example)

Site Scoring Criteria	KRI Weight	Low (1)	Moderate (2)	High (3)	Weighted Score
Competing Trial(s)	1.25		2		2.5
Limited Patient/Subject Population	1			3	3
Lacks a Dedicated Study Coordinator	1			3	3
PI Device Experience	1.5	1			1.5
<b>Total Risk Counts</b>					10
					<b>Risk Levels</b>
					Low ( $\leq 10$ )
					Moderate ( $11 \leq 20$ )
					High ( $\geq 21$ )

**RBM Tool Development II: Key Risk Indicators**

Another deliverable was identifying the KRI, as seen in Table 3. Additionally, each KRI was weighted such that when a KRI crossed the defined threshold (threshold of 1.0), the occurrence could be investigated and appropriate actions taken. For example, a study team may determine that after 10 enrollments, a monitor would schedule an on-site monitoring visit. Not all triggers require on-site visits. An example is open queries (assigned to the site) >60 days. This KRI was weighted at 0.1, meaning after 10 queries that remained open >60 days, the KRI triggered some action to be taken by the study team. In most cases this action was to contact the site to inquire about the open queries. In extreme cases a monitor may be deployed to the site to assist.

Table 3: Key Risk Indicators (Threshold = 1.0)

Key Risk Indicators	Weight
Enrollment	0.1
Adverse Event (AE) Occurrence	0.25
Protocol Deviations	0.2
Open Queries > 60 Days (Count)	0.1
Physician Decision to Withdrawal	1
Subject Death	1

**RBM Tool Optimization II: KRI Reset Dates**

The team encountered the issue of how to “reset” a site score after actions to address KRIs that crossed their respective threshold were taken. If a KRI were left to continue increasing, it would be difficult to distinguish at what point additional actions would be required without constantly referring back to the weighting to understand how many instances of KRI occurrence triggered crossing the threshold of 1.0. For example, if an on-site interim monitoring visit (IMV) took place after 5 enrollments, the enrollment KRI would be reset to zero, allowing the team to clearly identify when the subsequent 5<sup>th</sup> subject was enrolled (10<sup>th</sup> overall enrollment). Therefore, after the offending KRIs were investigated and properly

addressed, a KRI Reset Date was implemented so that only data from the reset date forward were considered.

An additional issue was subsequently identified with this method: If a KRI (e.g., Enrollment) crossed the threshold (1.0), while another KRI (e.g., AE Occurrence) was below the threshold (0.75), the AEs are not also reset to zero. Ideally, all contributing KRIs are evaluated prior to resetting the data. To address this, new reports were created to allow for individual KRI resetting. This allowed the teams to look at individual KRIs, as well as KRIs in aggregate, as many small KRI triggers may indicate larger issues overall.

### **RBM Tool Development III: Trigger Report Methodology**

The final deliverable was termed the “Trigger Report.” This report contained individual Site KRIs, Site Risk Assessment scores, and historical data graphs. The Trigger Report contains multiple sets of tables and graphs. Displayed as a dashboard (Figure 1), tables and graphs include a listing of Sites Reaching Threshold (crossing the threshold of 1.0); the number sites that have had a reset date between 30-60, 60-90, and >90 days; and the risk profile breakdown of participating sites.

Figure 2 shows average adverse events per subject at individual sites. This type of graph is useful for identifying outliers. For example, the average AE rate per subject for Site 2 is roughly four times greater than the study mean. This may not indicate an issue at the site if they happen to have a subject who had a difficult hospital stay unrelated to the study procedure. Or, it could be that if the AEs are procedure-related, the Principal Investigator (PI) performing the procedure may need retraining, or the procedure itself carries safety concerns (vs. the device). Conversely, sites with AE rates that are far below the study mean, such as Site 4, may be underreporting AEs. The benefit of visual tools is that they allow the teams to quickly identify and investigate outliers, and take appropriate actions as necessary.

Figure 1: Trigger Report – Dashboard Part 1

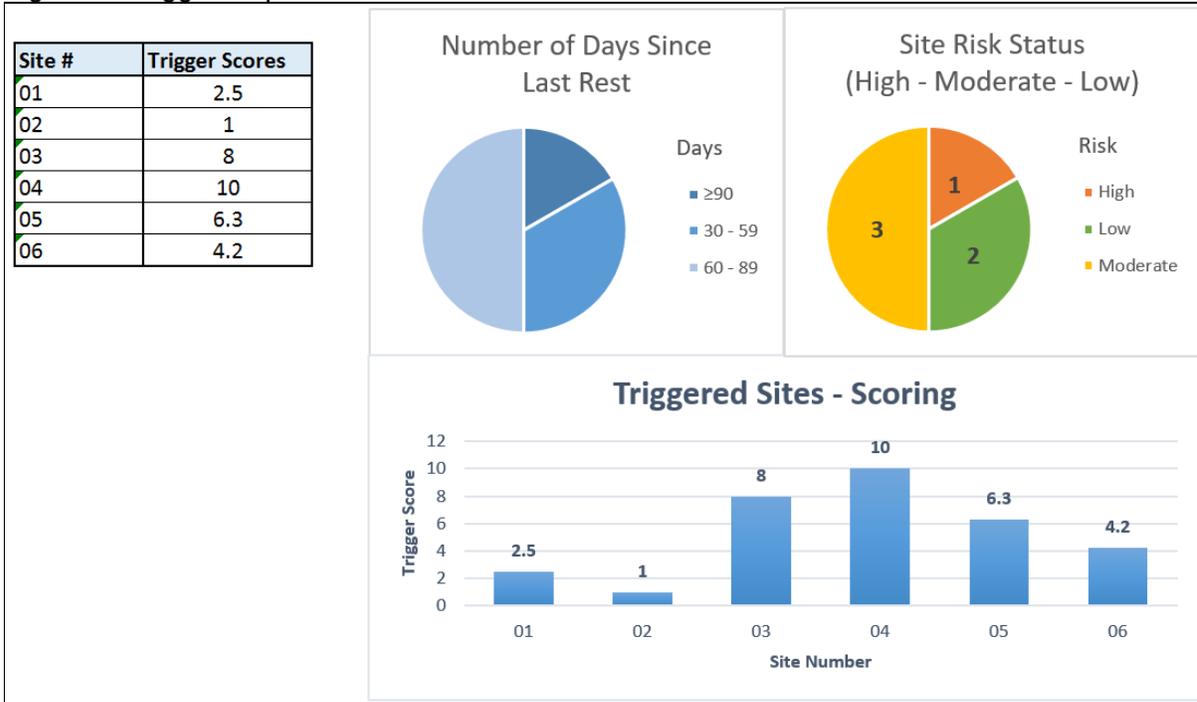
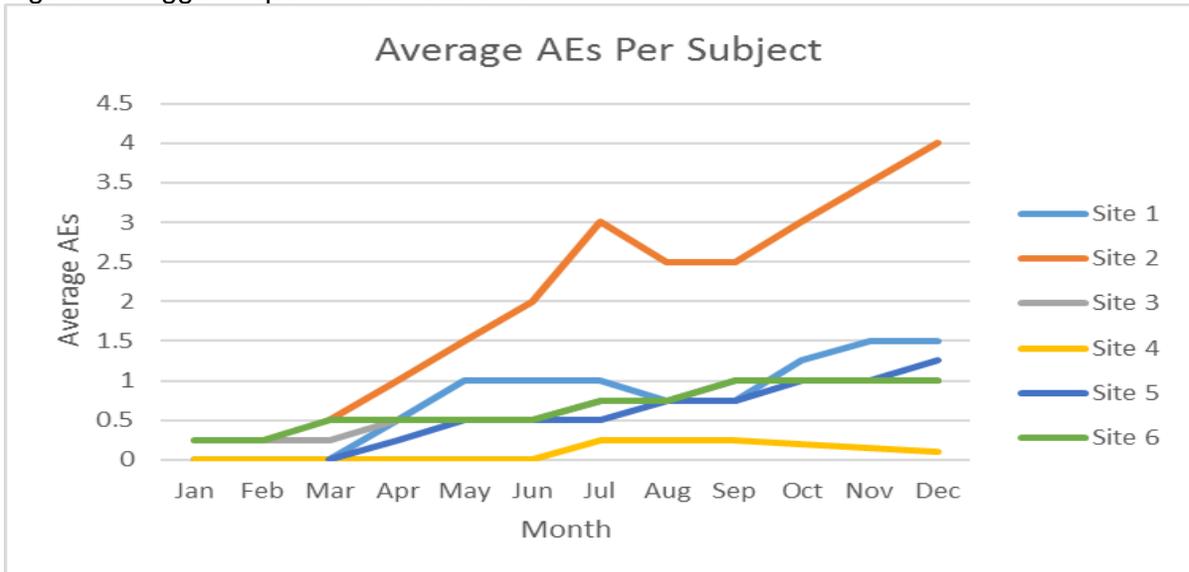


Figure 2: Trigger Report – Dashboard Part 2



V. RBM Summary

To date, the most commonly used clinical study monitoring approaches to ensure patient welfare and clinical study data integrity have been the resource-intensive process of:

1. Sending people to the clinical trial sites, repeatedly, throughout the course of a study
2. Manually inspecting Case Report Forms (CRF)s containing the clinical study data
3. Inspecting the source documents (often at 100% SDV), and
4. Conducting in-person interviews of PIs, study managers, and other study site personnel.

Clearly this is a very resource intensive process, which is costly in time, personnel allocation, and dollars. Further, this process is subject to time constraints, personnel availability, and data access problems. History demonstrates it also lacks scalability to account for the different risk levels of the products being evaluated. With so many resources being deployed for monitoring, both sponsors and regulatory bodies have elevated process execution as a focal point, thereby risking oversight of resultant data implications.

Going forward, regulators and industry agree that efficiency is needed in the monitoring process to manage resources and effort, while maintaining assurance that the data will be reliable and patients will be protected. FDA, Institute of Medicine (IOM), several clinical research organizations (CROs), and other organizations such as the Clinical Trials Transformation Initiative (CTTI) have initiated efforts to identify the tools that can be used to accomplish these goals. Targets for this work include the clinical study designs themselves, the means used to capture and maintain data, the potential to leverage technology to examine data, and increased site engagement in the monitoring process.

RBM is a critical approach being evolved to focus on the level of risk posed by the products and studies themselves. Understanding which study and product risks are the most important, and focusing efforts on managing those risks, are evolutionary steps to successfully advance the monitoring process, realize monitoring effort and risk mitigation economies of scale, ensure patient protections, and provide timely medical device access to patients and providers.

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