An influential 1999 report from the Institute of Medicine (IOM) of the National Academies discussed the quality of data obtained during biopharmaceutical clinical trials. Two quotes are of particular relevance in the context of risk-based monitoring (RBM). The first quote reads as follows:

A significant proportion of the time and expense of conducting clinical trials arises from the need to assure that the resulting data are accurate. Patients are selected, treated, and evaluated by a meticulous protocol, and results are recorded on standardized forms that are collected and analyzed by the sponsor or its designee. To ensure the validity and accuracy of the data, the pharmaceutical company periodically sends monitors to study sites to verify that patients are treated according to the study protocol and that the information is reported according to the study protocol. Monitoring alone can represent up to 30% of the costs of a clinical trial.

The second quote addressed the costs of obtaining “perfect” data, and the diminishing returns of attempting to do so:

Although data quality is a continuum, there can be no “perfect” data set; instead, there may be a decreasing marginal benefit from pursuing such a goal. Quality data would therefore be defined as data that sufficiently support conclusions and interpretations equivalent to those derived from error-free data.

Clinical research generates information, conclusions, and interpretations that provide the basis for rational decision-making. The IOM report’s viewpoint, therefore, is that quality data facilitate the same decisions being made that would have been made using perfect data.

A “reflection paper” issued by the European Medicines Agency (EMA) in August 2011 had a similar theme (i.e., facilitation of the development of a more focused, prioritized, and risk-based approach to quality management of clinical trials). Since absolute perfection in every aspect of an activity is rarely achievable, or can be achieved only by large increases of allocation of resources, practicality requires the establishment of priorities and of risk mitigation strategies for them.

The fundamental priorities of a clinical trial are the protection of subjects participating in the trial and the trial’s scientific and clinical objectives.
These priorities should then be reflected in the manner in which resources are assigned and in the control procedures employed.

A draft Guidance for Industry issued by the U.S. Food and Drug Administration (FDA) shortly after the release of the EMA’s reflection paper addressed RBM in detail, and brought this topic to the forefront of the regulatory landscape. Papers addressing various aspects and components of RBM (e.g., quality, source data verification [SDV], and centralized statistical approaches) can be found in the literature.

A review of the central tenets of the EMA and FDA documents was provided by Sax et al.2 Of relevance in the present paper is that, in partnership with its sponsors, the contract research organization (CRO) Quintiles had previously employed monitoring strategies that would fit within the broad rubric of RBM.

Following a brief section that recaps the fundamental tenet of the FDA’s guidance and provides an industry definition of RBM, this paper presents several case studies that exemplify important knowledge and experience gained to date from RBM, and takes discussions of this topic to the next level by explaining how RBM fits into the larger operational architecture of data-driven clinical trial execution.

**FDA’s Risk-Based Monitoring Guidance and an Industry Definition**

The FDA clarified to sponsors that it does not have a formulaic, one-size-fits-all view regarding the execution of monitoring activities during a clinical trial.

Noting that “This guidance is therefore intended to clarify that risk-based monitoring, including the appropriate use of centralized monitoring and technological advances (e.g., e-mail, webcasts, and online training modules), can meet statutory and regulatory requirements under appropriate circumstances.”4 The guidance also comments as follows:

There is a growing consensus that risk-based approaches to monitoring, such as focusing on the most critical data elements, are more likely to ensure subject protection and overall study quality, and will permit sponsors to monitor the conduct of clinical investigations more effectively than routine visits to all clinical sites and 100% data verification.4

The guidance provides a meaningful, but relatively complex definition of RBM. A more succinct industry definition was provided by CenterWatch: RBM is “the concept of monitoring trials electronically from a central location and sending monitors to sites only when necessary rather than every four to six weeks.”

**Developing an Approach to Risk-Based Monitoring: Three Case Studies**

Because of its awareness of the concept of RBM for many years, Quintiles has progressively and iteratively developed its current approach to data-driven trial execution. The three case studies provided below describe the strategies employed in each study, and the lessons learned concerning what worked well and which components needed additional refinement before their employment in subsequent studies.

**Case Study 1**

This case focuses on the lesson learned from a risk-based model in which the approach was to reduce SDV in a late-phase outcomes trial. A number of options for reducing SDV were considered. The monitoring option chosen involved conducting SDV of a subset of selected subject visits only, chosen at random. The normal chronological sequence of monitoring visits and full SDV of an entire subject’s source data in sequential order (Visit 1, Visit 2, Visit 3, etc.) allows the detection of compliance issues over the full sequence of protocol assessments. This approach detects possible misunderstandings or errors in process as the protocol application unfolds, and thus reveals the underlying trends of compliance at the site.

In our case study, where selected subject visits were reviewed by SDV, we learned that we needed to refine the compliance monitoring, as this approach did not allow effective trend detection at the time. Trends provide very important predictive information, and monitoring them via centralized oversight of sites’ compliance through aggregated data has now become a core component of RBM.

**Case Study 2**

The experience gained in Case Study 1 led us to articulate each of many triggers for monitoring visits, and to deploy these triggers in a situation represented by the present case study, which covers an entire development program across a single compound. It was soon realized, however, that we had actually included considerably more than the optimal number of triggers for targeted manual monitoring, leading to an excessive amount of “noise” and loss of efficiency in the data collected.

The lessons learned here were threefold:

- Identification of the critical data requiring maximum attention is crucial;
• A more simple approach identifying these items in advance and minimizing the total number of triggers is essential; and
• A better, electronic way of working (i.e., automating and aggregating data in a model we call Infosario) was likely to be the optimal approach.

The Infosario model is one that obtains the correct balance between the standardization, or industrialization, of the process (probably around 80% of the model can be automated and is consistent across studies) and the customization needed for each study on a trial-by-trial basis. It also allows for critical modifications to be made from time to time, as needed in a particular study or development program.

**Case Study 3**

All of the lessons learned from employing RBM in previous trials were incorporated into our approach to the trial of interest in this case study, which involved the examination of morbidity and mortality outcomes in a large population. It had become clear that a “smarter” approach was needed—one in which a carefully chosen and small, but critical, set of thresholds was developed and actively monitored to address any backlog in SDV via automated triggers and consequent deployment of resources to respective sites.

The trigger thresholds were very clearly articulated, based on knowledge at the time the trial commenced, and we initially thought that, once in place, these thresholds would be appropriate throughout the entire study. However, concerns over the number of monitoring visits per unit of time became apparent approximately six months into the study, and it became clear to us that the triggers needed to be regularly rearticulated as the study progressed, to avoid overburdening the system and to ensure the optimal deployment of monitoring resources.

**Current Approach to RBM: Data-Driven Trial Execution**

Based on a decade of experience and the lessons learned during that time, we currently view RBM as one important element of a data-driven approach to clinical trial management and execution. By unlocking, using, and integrating the full value of aggregated data with proven processes and therapeutic expertise, we can improve data quality, enhance the safety of trial participants, shorten trial cycle times, achieve data lock more efficiently, streamline regulatory submissions, and shorten the time to market.

Data-driven trial management and execution starts with an in-depth assessment of scientific and operational risk. Considerations include determining the appropriate SDV goal, the thresholds to be set for which critical triggers, and which global regions, sites, and participants should be included.

While some elements of the overall process can beneficially be standardized, both sponsors and their CRO partners are better served when studies are scrutinized and analyzed to determine the best approach.

**Data-Driven Trial Execution**

Based on our extensive experience with RBM, we have developed an approach that we call data-driven trial execution. Its operational architecture, depicted in Figure 1, contains three key components:

- risk assessment—an initial in-depth assessment, followed by ongoing assessment;
- data surveillance; and
- dynamic monitoring.

**Risk Assessment**

With regards to RBM, there are three types of risk:

- scientific risk—the objectives listed in the trial’s protocol;
- the patient pathway—the means by which patients with the disease or condition of clinical concern will be recruited to become participants in the trial, and then retained in the trial to complete their full participation; and
- operational risk—making sure that all operational aspects are executed optimally.

The aforementioned team of relevant personnel should therefore conduct an up-front risk assessment of each trial, whereby the right questions are asked and answered. Following this initial analysis, risk is then reassessed and actions are recalibrated throughout the life of a trial via the next two components—data-driven surveillance and optimized monitoring.

**Data-Driven Surveillance**

Advancements in technology and workflow, such as those offered by the Infosario platform developed at Quintiles, facilitate data review in near real-time throughout the life of a study to initiate the right action at the right time...
for efficient trial management. Risk is constantly reassessed, allowing monitoring to be adapted and optimized throughout the trial. For example, data indicating an atypical level of protocol deviations will trigger a site visit.

**Dynamic Monitoring**

Dynamic monitoring, which is tailored on a trial-by-trial basis having evaluated the risks, comprises deployment of the right type of monitoring (i.e., onsite, remote, centralized) at the right time to oversee sites, data, trial participants, and events that require more attention and focus. A monitoring model should take into account the type, frequency, and intensity of monitoring needed to guarantee participant safety, data integrity, and quality, while also ensuring that the study objectives are met. This approach allows the focus of intensive monitoring to be placed on the sites and the study aspects that represent the greatest risk.

**Underlying Technology**

Knowledge-driven trials are based on experience, scientific expertise, and understanding. First, study design needs to be data-driven; there then needs to be integration between design and execution, leading to a new way of building out a complete portfolio.

Infosario is the knowledge engine that powers data-driven trial execution at Quintiles; it seamlessly integrates data, the company’s systems and processes, and therapeutic expertise. Following data integration, triggers and alerts initiate the right action at the right time for safe, efficient, and high-quality trial management.

Infosario enables sponsors to drill down into data to make important connections, recognize current and emerging trends, and, most importantly, make more informed decisions. For example, data indicating an atypical level of protocol deviations at a given site will trigger a site contact. The benefits of knowledge-driven trials include:

- Faster, better informed decisions—immediate access and interpretation of trial, patient, and other relevant data;
- Transparency—a data-driven, near real-time view into data;
- Quality—maintains quality, patient safety, and regulatory compliance; and
- Efficiency and productivity—reducing the recourses, time, and cost required.

**Risk is constantly reassessed, allowing monitoring to be adapted and optimized throughout the trial.**

**Concluding Comments**

Following the 1999 IOM report discussing the quality of data obtained during biopharmaceutical clinical trials, Quintiles has more than a decade of experience with RBM. Lessons learned concerning the optimal number of thresholds for triggered monitoring; the need for not only precise initial articulation of these thresholds, but also their continuing rearticulation throughout a study; and the benefits of an automated approach have proved extremely effective in refining our approach to RBM and its use within our data-driven trial execution strategy.

**References**