Seeing Around Corners:

Risk Assessment Is the Foundation of Risk-Based Monitoring

By: Jeff Fetterman, President ParagonRX, an inVentiv Health Company,
Michael Macri, Director, Strategic Services, inVentiv Health Clinical

The Goal: Reducing Uncertainty

It stands to reason: You can't properly monitor risk until you've first identified and assessed potential risk. There is consensus among regulators and industry leaders that risk assessment is the foundation of all subsequent planning for risk-based monitoring. The U.S. Food and Drug Administration (FDA), for instance, indicates "sponsors should perform a risk assessment to identify and understand the nature, sources, and potential causes of risk that could affect the collection of critical data or the performance of critical processes."[1] And the position of the European Medicines Agency (EMA) is that "the identification of priorities and potential risks should commence at a very early stage in the preparation of a trial, as part of the basic design process…"[2]

At this writing, the life sciences industry is eagerly awaiting approval of the first new drug application to be based on RBM, so there are no test cases yet for how regulators evaluate data monitored by RBM plans in the approval process.

In the absence of a standardized, systematic approach to risk assessment as the foundation of RBM, there will always be considerable uncertainty as to regulators' response to any given strategy. However, if a regulator asks how you know that you are taking the right steps to ensure data integrity and protect patient safety, you can answer the question quite confidently when you've begun with a robust risk assessment guided by quality risk management standards such as ICH Q9.

Thus, a proper risk assessment not only minimizes uncertainty in a trial, but also the uncertainty of regulators' response to your monitoring approach.

A Word on RBM

RBM is a systematic and adaptive approach to clinical trial monitoring that relies on innovative strategies to identify and manage risk throughout the life cycle of the trial. The goal is to enhance patient safety and data integrity by focusing attention on those areas that are critical to the reliability of study results. Any monitoring strategy should be geared to the specific trial protocol, although there are four broad components to every effective RBM program: systematic risk assessment, remote and centralized monitoring, a strategy for on-site monitoring, and alerts and triggered workflows. (See Figure 1.)

With regulatory authorities, industry associations, and leading organizations (such as TransCelerate BioPharma) all supporting the use of risk-based monitoring (RBM) in clinical trials, the case has been made quite convincingly for designing monitoring plans that are "tailored to the specific human subject protection and data integrity risks of the trial."[1] Indeed, an informal poll by inVentiv Health Clinical suggests that approximately half of sponsor organizations have begun to experiment with RBM.

Yet many of these first experiences have used informa l— rather than standardized — approaches to the very first step in the process: assessing the risks that are to be mitigated through monitoring. Here we outline a systematic and rigorous process to assessing risk, using quality risk management principles, that will increase the likelihood that your RBM approach will pass regulators' scrutiny.

Figure 1: Components of a Risk-Based Monitoring Program

Sponsors and clinical research organizations (CROs) are moving quickly to implement RBM, with regulatory authorities' encouragement and leadership from TransCelerate BioPharma Inc., a consortium of leading life sciences manufacturers dedicated to improving R&D processes. Even so, there persist some misconceptions about RBM that deserve to be corrected.

These include:

- *RBM eliminates or substantially reduces monitoring efforts.* An RBM approach—founded on a systematic risk assessment — will likely change *what* you monitor and perhaps how you monitor it, but it doesn't *ipso facto* reduce the effort involved. It does not, for example, automatically lead to a reduction in site data verification (SDV); an RBM plan could, conceivably, still call for 100 percent SDV.

- *RBM is a sure way to lower costs.* It is true that RBM presents a cost-cutting opportunity if the plan more efficiently uses human resources, such as clinical research associates (CRAs) and site monitors. It is ill advised, however, to adopt RBM with the specific goal of cutting costs. There will certainly be a higher suspicion of bias on the part of regulators toward RBM plans in which the driving force was cost — rather than risk — reduction.

- *RBM monitoring is risky monitoring.* Ironically, this impression persists, even though the very purpose of RBM is to reduce risk. It likely stems from an entrenched belief that 100% SDV is the gold standard of monitoring, while RBM often calls for alternative approaches. In reality, by properly assessing risk and applying the most appropriate risk-based monitoring strategy, threats to patient safety and data integrity can be foreseen and so either avoided or mitigated.

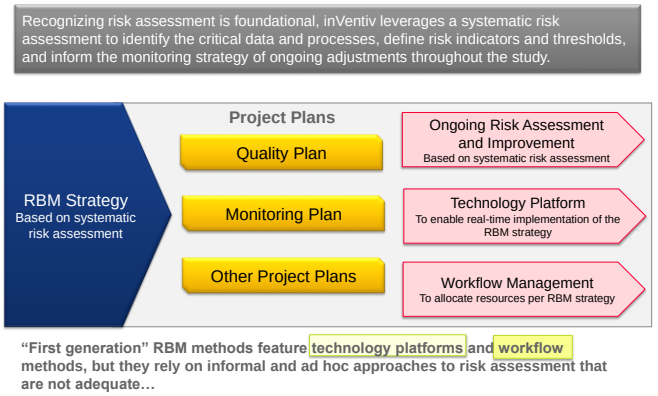
- *RBM can be completely automated.* Technology, of course, plays a major role in RBM, with centralized systems used to examine trial data to detect anomalies and spot trends. Software is clearly needed to eliminate the manual effort in consolidating, analyzing, and reporting data. Yet, technology is certainly not the whole answer; once potential problems are detected, they require further investigation and possible corrective action through human intervention.

"Our experience with sponsor companies suggests that RBM is gaining momentum," notes Michael Macri, director for Strategic Services at inVentiv Health Clinical. "Companies are eager to see if they can use RBM to improve trial quality while also using resources more efficiently. We believe that both goals are achievable, provided that sponsors follow a monitoring plan structured according to a thorough risk assessment."

The Scheme of Things

Risk assessment is the first step in building quality into trial execution and precedes risk monitoring, as illustrated in Figure 2. The goal of risk assessment is to proactively find and mitigate — or, ideally, eliminate — unwanted variability in all stages of the clinical trial.

Figure 2: Risk Assessment as the Foundation for Project Planning



A systematic assessment of risk:

- Defines the data and processes that are critical to ensuring data quality and patient safety.
- Identifies the risks that could degrade the quality of data or patient safety.
- Establishes interventions to minimize those risks.
- Defines risk indicators and risk thresholds to enable continuous monitoring.

The risk assessment will inform the RBM strategy, which in turn provides input into the trial's quality plan, monitoring plan, and other project plans.

While necessary, the initial assessment is not sufficient for a successful RBM implementation; the process must be sustained through ongoing review and continuous improvement. Implementing a risk-adapted plan also calls for a technology platform that can provide real-time information and requires careful allocation of resources.

A common mistake with first-generation RBM plans has been to focus on the later stages of applying technology and managing the workflow methods, without first giving the risk assessment its due diligence through scientific methods. *Ad hoc* or informal approaches to risk assessment compromise the foundation on which the RBM strategy is built.

When risk is assessed properly through the use of accepted, validated methodologies, the exercise:

- Minimizes surprises by anticipating problems.
- Reduces potential errors in hazard identification.
- Supports effective plan development and execution.
- Provides the opportunity to optimize resource monitoring costs.
- Is reproducible and defensible in the event of regulatory inquiry.

A Best Practice Approach

As the first vital step in RBM, risk assessment warrants a highly systematic approach. One federal agency put it quite succinctly: "Risk assessment is, to the highest extent possible, a scientific process."[3] Complete "how-to" instructions would require volumes and so are beyond the scope of this paper; however, they can be described briefly in five high-level steps. (See Figure 3.)

1. **Define the trial process and risks to be addressed.**
   While it may sound simple, identifying the scope of the risk assessment is challenging yet one of the most critical aspects of the process. It is possible to look at risks associated with aspects of the trial that extend well beyond data integrity and patient safety — indeed, to adopt a quality-by-design approach to the entire trial. In early attempts at assessing risk, however, it is advisable to maintain a compact, manageable scope. Over time and as a team gains experience, the scope can be broadened to include multiple protocols within a study program or additional geographies.

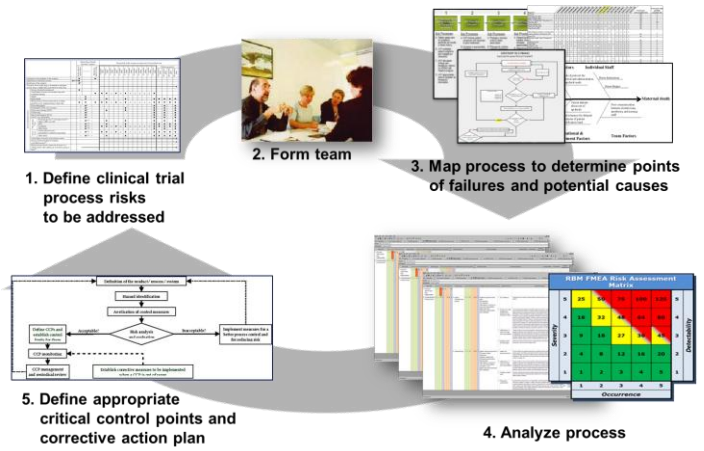
2. **Form a cross-functional team to guide the process.**
   Members of the team should have deep knowledge of the trial process and bring different perspectives on where problems have arisen in the past. Together, they should have the expertise to anticipate what could go wrong in the future. The team will need a software tool to facilitate communication and support data analysis.

3. **Map out the trial process.**
   The cross-functional team should illustrate the entire study process, identifying the points at which failures could occur and noting the potential causes. Failing to map the process relegates the risk assessment to a more informal or ad hoc approach that is less comprehensive.

4. **Analyze the risks.**
   Next, the team should score the risks that have been identified in the trial map and attach a priority to each hazard — a particularly difficult exercise. The scoring uses scales for assigning quantitative levels for the severity of unwanted outcomes resulting from a risk, the likelihood of a risk occurring, and the ability to detect when a risk occurs. The resulting score is used to prioritize risks and direct appropriate monitoring resources where they matter most. Every decision the team makes should be archived for future reference.

5. **Define the Critical Control Points and the Corrective Action Plan.**
   The final steps are to: 1) establish interventions that minimize the occurrence of risks and 2) identify the key risk indicators and thresholds that trigger corrective actions in the event such risks occur.

Figure 3: Risk Assessment Process Activities



Standard Methodologies

Fortunately, there exist well-established quality risk management methodologies to guide the team's work in identifying the most important risks to be managed — methodologies that regulators, in fact, recognize, recommend, and in some cases, had a hand in developing. The ICH Q9 Quality Risk Management document[4] provides clear principles for identifying, assessing, and controlling risks. The following validated methodologies have all been accepted by regulatory authorities as the basis for approvals in other healthcare categories and industries and will help the team proceed systematically:

- *Root Cause Analysis*. This provides a formal approach to examining issue lists and failure logs from other trials to spot the problems that occurred and determine what caused them. Obviously, this is a retrospective analysis that requires comprehensive records of historical failures and the means to interrogate the data. When the upcoming trial is in a new therapeutic area for which the company does not have historical data to draw upon, it will need to call in outside experts who can offer expertise in the therapeutic area.
- *Failure Mode and Effects Analysis (FMEA)*. This step builds upon the understanding of what has happened in the past to predict the points of potential failure in the upcoming trial. In performing an FMEA, the team will pinpoint those critical processes and data inputs that need to be managed in order to mitigate issues. At this stage, risks are prioritized and interventions prescribed. The volume of data included in such an analysis benefits from the use of a database to enable appropriate evaluation.
- *Hazard Analysis and Critical Control Point (HACCP) Management*. This is an active process for establishing and monitoring the thresholds for each key risk indicator in order to detect and eliminate the occurrence of hazards identified by the prospective analysis. In the course of the study, exceeding these thresholds triggers corrective actions to ensure data integrity and patient safety.

The output of this work should include:

- An illustration of the clinical trial process, highlighting areas that could compromise human subject safety or data integrity.
- Prioritized lists of risks and interventions to minimize those risks.
- Details on critical control points with the associated tolerance thresholds, triggers for intervention, and corrective actions;
- Performance metrics to guide continuous quality improvements.
- "Mapping" of risk assessment findings to the quality risk management plan, monitoring plan, and project plans.

These materials will not only be used in developing the operational plans for the trial, but can also serve as a body of evidence for defending the company's approach to regulators. They should be reflected in the company's project management system for the trial, and updates to, and learnings from, the process should be archived for future reference. In this way, the company should gain institutional knowledge over time and become increasingly adept at systematic risk assessment.

Key Takeaways

A systematic risk assessment should drive the development of your monitoring strategy. It should be a foundation and first step, not an afterthought.

Established methodologies for quality risk management should be used to perform your risk assessment. Doing so will reduce the uncertainty of regulators' response to your RBM strategy.

Those responsible for performing the risk assessment should represent a cross-section of clinical and operational functions.

- Assessing risk is both a retrospective and prospective exercise that relies on the availability of historical and real-time data.
- It is important to carefully manage the scope of your initial attempts at risk assessments.
- A desire to reduce costs should not be the primary driver of adopting a risk-based approach.
- The monitoring strategy must be designed for the unique needs of each trial, as defined by the risk assessment.

CONCLUSION

There is an expectation and early evidence that risk-based monitoring can produce significant improvements in trial quality and productivity, both of which have been static for some time. The key to realizing these benefits is to begin the trial planning process with a systematic and structured risk assessment using standardized methodologies.

As the industry gathers experience in RBM and awaits the first drug approvals based on clinical trials using RBM, it can draw confidence from using the risk assessment methodologies that regulators themselves support.

REFERENCES

1. U.S. Department of Health and Human Services. *Guidance for Industry: Oversight of Clinical Investigations* — A Risk-Based Approach to Monitoring, August 2013.

2. European Medicines Agency. *Reflection Paper on Risk Based Quality Management in Clinical Trials*, November 2013.

3. U.S. Environmental Protection Agency. "What is risk assessment?" epa.gov/riskassessment/basicinformation.htm#arisk

4. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. *The ICH Harmonized Tripartite Guideline, Quality Risk Management, Q9, Step 4 version*, November 9, 2005.

inVentiv Health clinical

inVentiv Health Clinical is a leading provider of global drug development services to pharmaceutical, biotechnology, generic drug, and medical device companies, offering therapeutically specialized capabilities for Phase I–IV clinical development, bioanalytical services, and strategic resourcing from a single clinical professional to an entire functional team. With 6,500 passionate employees supporting clients in more than 70 countries, inVentiv Health Clinical works to accelerate high quality drug development programs of all sizes around the world. www.inventivhealthclinical.com