Managing Clinical Trial Risk: It's a Tough Job, But *One* Person Has To Do It

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Since the U.S. Food & Drug Administration published its guidance on Risk-Based Monitoring approaches to clinical trials, sponsors have demonstrated a mixture of interest in, and trepidation toward, focusing their oversight activities on those areas that present the greatest risk to human safety and data integrity. The methodology is new enough that best practices are still being developed by sponsors and Clinical Research Organizations alike. One clear recommendation that is emerging, however, is to assign the ongoing responsibility of managing a trial's risk to a new member of the study team: the Clinical Risk Manager. The creation of this dedicated role ensures that trial risks are assessed and mitigated systematically by an expert with the express responsibility and authority to do so. The following paper explains the need for this position, what should be expected of a Clinical Risk Manager, and how the role can operate effectively within the study team.

AN OVERVIEW OF RBM

The purpose of any risk management plan is to actively find and mitigate sources of risk, ideally by eliminating unwanted variability in all stages of a process. In clinical trials, the emphasis is on identifying, reducing, and monitoring risks to patient safety, data integrity, regulatory and protocol compliance, and project scope (both budget and timelines).

Risk-Based Monitoring (RBM) is an innovative strategy for managing risk that *concentrates attention on those areas that are critical to the reliability of the study results*. By properly assessing risk and applying the most appropriate monitoring strategy according to risk priorities, threats to patient safety and data integrity can be foreseen and either avoided or mitigated because they are caught early. While the chosen strategy should be geared to the specific study protocol, there are four components to every effective RBM program:

- **Systematic risk assessment**
  As the foundation of all subsequent steps in RBM, risk assessment will inform the RBM strategy, which in turn guides the trial's Quality Plan, Monitoring Plan, and any other Project Plans. Assessing trial risks involves defining the data and processes that are deemed critical to patient safety and data quality, identifying the risks that could degrade either, establishing processes to minimize those risks, and setting risk indicators and thresholds that will trigger an investigation and corrective action.

  The goal of the risk assessment exercise is to prospectively identify and control potential issues that may be encountered through the trial process. Yet, no process—no matter how thorough—will be able to eliminate all risk. While a systematic risk assessment methodology such as Failure Mode and Effect Analysis (FMEA) may identify a majority of a trial's potential risks, new, unidentified issues may manifest themselves during the course of the study. This speaks to the ongoing nature of risk management and the need to be prepared to address issues as they emerge, even with the implementation of a well-conceived, Quality and Risk Management Plan (QRMP).
  A *systematic* risk assessment also addresses the need to minimize the

The Tools of the Trade

Clinical Risk Managers (CRM) need to be familiar with a battery of analytical tools and techniques to perform the job, which is why certification as a Risk Management Professional is beneficial. The ICH Q9 briefing pack, "Annex 1: Risk Management Methods and Tools," provides a good overview of the facilitation tools, methodologies, and statistical processes that are the CRM's stock in trade. Facilitation tools that can be used to support risk identification include flowcharts, check sheets, process maps, and cause and effect diagrams.[3] Also, TransCelerate has created an *ad hoc* Risk Assessment Categorization Tool (RACT) to help identify and categorize events that may cause risk.

Useful methodologies (which form a rich alphabet soup) include:

- Root Cause Analysis (RCA) to retrospectively identify the root causes of failure.
- Failure Mode Effects Analysis (FMEA), an approach to prospectively analyze potential failures and associated causes, prioritizing risk, and identifying interventions.
- Failure Mode, Effects and Criticality Analysis (FMECA), which additionally links severity, probability, and detectability to criticality.
- Fault Tree Analysis (FTA), uses a causal diagram to identify possible failures in a system.
- Hazard Analysis and Critical Control Points (HACCP), a systematic approach to actively monitor key risk indicators to detect issues and address through corrective action.
- Hazard Operability Analysis (HAZOP), which is a brainstorming technique useful in identifying hazards.
- Preliminary Hazard Analysis (PHA), a technique for applying prior experience or knowledge of a hazard or failure to identify future hazards.
- Risk Ranking and Filtering, a way of evaluating risk factors to produce a relative risk score that can be compared, prioritized, and ranked.

regulatory uncertainties associated with employing RBM in these early years of the industry's adoption. Currently, there is no RBM precedent to know what regulators will require to answer the question: "How can the sponsor demonstrate that it identified, controlled, and monitored the relevant risks to data integrity and human safety?" Fortunately, ICH Q-9 Quality Risk Management offers a roadmap to risk managers on how to systematically assess, control, and monitor risks. Regulators already accept or endorse these methods as ways to control risks to quality in the manufacturing of products. It is, therefore, highly likely that they will accept them to control risks to data integrity in RBM.

- **Centralized monitoring**
  Centralized monitoring, performed in a location other than at the investigational site and performed in near real time, uses a combination of expert oversight, electronic systems, and statistical analyses to examine incoming trial data and spot anomalies and trends. Once potential problems are detected, they require further investigation and possible corrective action.

- **On-site monitoring**
  Centralized monitoring does not replace on-site monitoring, but supplements and often directs it by suggesting what specific sites require attention from Clinical Research Associates (CRAs) because they are identified as higher risk. The process can further specify what areas should be investigated during such visits. In many cases, centralized monitoring *does* reduce the level of on-site monitoring required, but that is not a foregone conclusion.

- **Alerts and triggered workflows**
  The centralized monitoring process relies heavily on software programs to flag any deviations in trial data that are outside of a prescribed range or that form a specific pattern. This generates an alert, signaling the need for further investigation and possible intervention. Thus, while technology is a great aid to RBM, it is only part of the story. Human oversight, analysis, and intervention are critical.

NEED FOR A DEDICATED RISK MANAGER

To be effective, risk management—encompassing risk assessment, monitoring, and mitigation—must be systematic, dynamic, and ongoing. It must be factored into all trial activities—incorporated into early plans and continuously addressed through all stages of trial execution.

As stated, some unforeseen risks will emerge over the course of the trial, requiring prompt attention and timely corrective actions. Early identification of a weakness is critical to eliminating systematic error that could corrupt clinical trial data and lead to costly delays at best or at worst, the creation of significant safety concerns or failure to achieve the clinical trial objective. What is more, the experience from each trial should be used to build a body of organizational knowledge and best practices that facilitate continual improvement in how RBM trials are conducted and monitored.

While controlling risk concerns the entire project team, unless one individual is designated to serve as the functional "owner" of the risk management process, it is unlikely to become a central, guiding principle in how a study is conducted.

Any or all of these tools (as well as many others) may be used to develop the QRMP, which the CRM should author, reference, and keep current. This vital document drives trial activities by laying out the overall risk of a study, identifying the critical risk and trial priorities, establishing ranges and tolerance limits around key risk factors, and prescribing how significant and serious risks are to be mitigated.

Keys to Success

Implementing RBM, just as with other organizational initiatives, must be a carefully orchestrated process that incorporates the best practices of change management. Chief among these is visible sponsorship from senior leadership. An executive either at the Board or C-Suite level should:

- Set forth the vision for a quality-instilled culture and a risk-based approach to managing trials.
- Make a long-term commitment to the process. It will take time for quality and risk management principles to evolve and grow.
- Pave the way for any difficult organizational changes to roles and processes.

Such executive sponsorship will enable CRMs to be successful, leaving no questions as to the organization's commitment to the quality/risk management process or the CRM's mandate and authority.

A Case in Point

In one real-life situation, a CRM working on a large Phase III study spotted a recurring error related to the primary efficacy measure that determined cohort assignment and which was taken at the time of randomization. This error had the potential to become systematic and could have put the entire clinical trial in jeopardy. Fortunately, this error was detected early through the CRM's prompt and close monitoring of the clinical trial data, and an action plan was put in place to mitigate the risk. In this case, the monitors and the clinical site personnel were retrained on the procedures, averting a major issue with trial execution.

Keeping the trial team's attention on risk throughout the study requires that someone coordinate the effort across functions and serve as a clearinghouse for all risk-associated activities. And that, in turn, calls for specialized expertise (a blend of trial management and risk management experience) and constant attention—typically more than what either the Project Manager (PM) or the Clinical Monitor could provide.

Building responsibility for risk assessment and creating and implementing the QRMP into an existing job is to give it short shrift. It's been said, "If you treat risk management as a part-time job, you might soon find yourself looking for one."[1]

One progressive solution is to carve out the responsibilities related to systematizing risk management to one person: a Clinical Risk Manager. This is in line with a recommendation from TransCelerate BioPharma Inc, a non-profit consortium of 19 biopharmaceutical companies. The organization has stated that although risk identification and assessment should be a cross-functional activity, "it is essential to have an individual who understands the overall process to facilitate the appropriate risk discussions".[2]

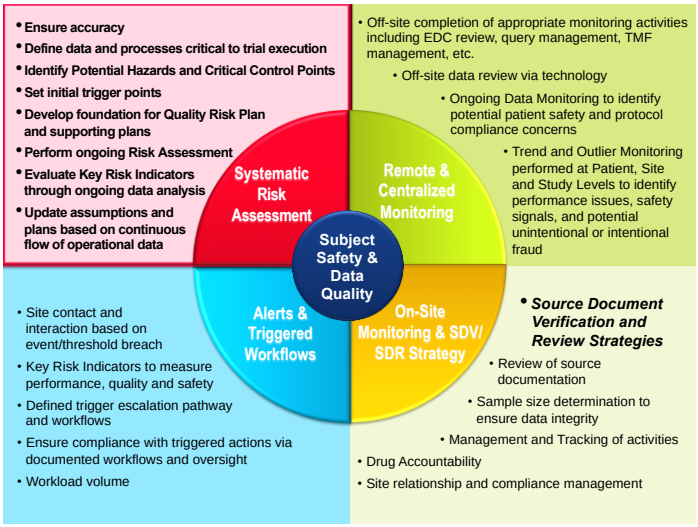
ALL THINGS RISK-RELATED

What, precisely, would be a Clinical Risk Manager's mandate? Primary responsibilities should include:

- Leading the project team in identifying key, study-specific risks (using a validated risk assessment tool) and key risk indicators as well as developing the threshold values that will trigger the examination of a finding.
- Creating and maintaining the QRMP, a study-specific plan that aligns all the associated functional plans across risk and critical data and processes.
- Working as part of the trial team to develop the study's Quality and Monitoring plans, under the direction of the Project Manager. Both of these flow from the risk assessment.
- Communicating and coordinating activities with the study team on study- and site-specific risks.
- Interpreting the metrics, performance indicators, and trends that emerge from centralized monitoring within and between programs to ensure proactive decision making and interventions. The key to performing RBM efficiently is to ensure a continuous flow of study data that are monitored for trends to enable real-time decision making and actions.
- Developing and recommending risk mitigation strategies by working with functional leads to document and escalate issues identified, develop and track strategies to mitigate them, and conduct root cause analysis to institute corrective and preventative action plans.
- Setting an example to others—and training those on the study team—in the mindset and practices that will instill quality across a given study and throughout the culture.

Figure 1 indicates which activities in the four components of a Risk-Based Monitoring Program would logically fall under the responsibility of a Clinical Risk Manager.

Figure 1: Components of a Risk-Based Monitoring Program



To perform these duties, a CRM must have a unique blend of skills and experience—such that finding qualified candidates for the position could be a recruiting challenge in many organizations. We recommend that a CRM bring to the position:

- Strong experience in clinical research, specifically via a leadership role on a clinical research team
- Specialized knowledge of the processes and tools related to risk assessment and mitigation, especially those tools highlighted in the Tools Annex of ICH Q-9, Quality Risk Management. One indication of this is certification as a Risk Management Professional
- The ability to analyze and interpret data using clinical data tools and technologies
- Strong interpersonal and leadership skills, as a CRM must coordinate a multi-functional team to deliver results and model quality/risk management practices for others

THE CRM AS A LYNCHPIN

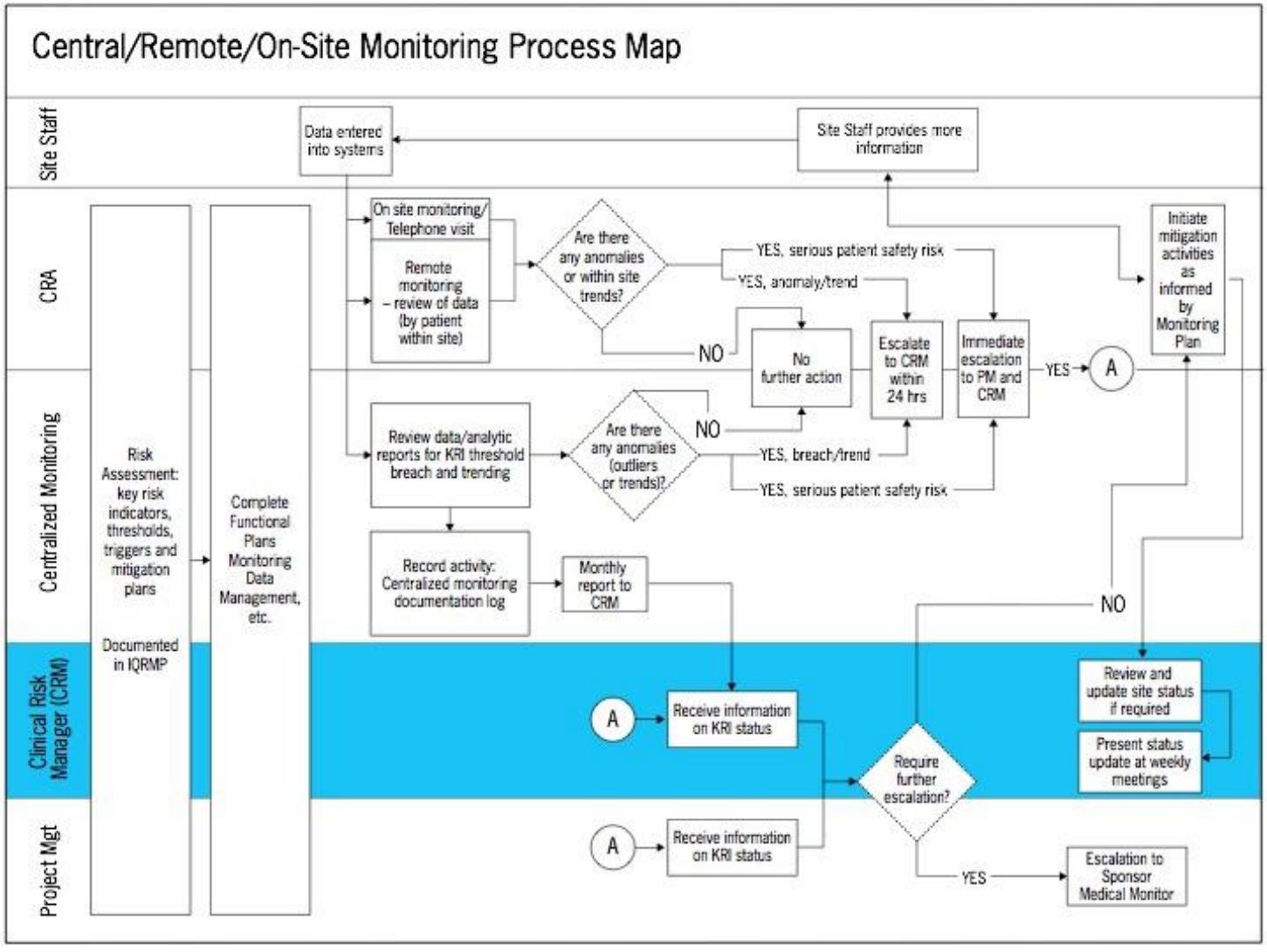
Creating a new role dedicated to risk management could cause some confusion with other key positions concerned with trial quality; it is, therefore, necessary to be very clear on the boundaries of responsibility between the CRM, the Project Manager, and other monitors. These include the Central Monitor, any Remote Monitors working away from the clinical site and On-Site Monitors, in particular.

One effective model is to have the CRM report to the Project Manager of the study team and to have the Central Monitor managed by a department director, but with functional accountability to the CRM on assigned projects. Similarly, the Subject Matter Experts (which again report via a dotted line) may include a statistician, clinician, and risk assessment expert. At the same time, the CRM must maintain a close working relationship with the Clinical Team and Data Services Team Leads. The CRM is, in fact, the one person, other than the Project Manager, who interacts with all functions supporting a study.

In the course of ensuring patient safety and the delivery of high quality clinical data, the CRM will be called upon to coordinate plans and activities between all of the members of the project team. (See Figure 2) The Central Monitor reviews the data from a remote location in real time, as it is entered by site personnel, using analytics and comparing values across sites for trends, outliers, inconsistencies, and unusual patterns. The CRM then interprets the central Monitoring outcome reports for the actual risk represented and determines how any situation that arises should be handled. At the same time, the CRM determines whether any risks that arise have been previously identified, or if they represent a totally new risk that must be added to the QRMP.

The CRM then must notify the Remote Monitor and the On-Site monitor of any identified risk if further resolution is required. Meanwhile, the Remote and On-Site Monitors conduct monitoring visits according to the schedule in the monitoring plan and report with-in-site risk level escalations to the CRM for interpretation and mitigation. Multi-part active communication, tracking and documentation are critical.

Figure 2: Central/Remote/On-Site Monitoring Process Map



MEASURING SUCCESS

What types of goals should be established for the role, particularly as the CRM must rely on others to analyze data and spot anomalies as well as to execute mitigation tactics? And, how should the CRM's performance be evaluated? Clearly, there can be no expectation that the CRM can prospectively identify and control ALL risk. Performance goals for the position can be created around:

- Developing a well-written and effective Integrated Quality Management plan
- Implementing timely risk-mitigation strategies
- Promptly identifying significant quality issues
- Assessing risk effectively/comprehensively—to develop the most appropriate monitoring strategy, identify key risk indicators and thresholds
- Eliminating systematic error in a clinical trial
- Increasing the efficiency of cycle times, e.g., data entry timeliness, query turnaround, database lock
- Eliminating re-work
- Using monitoring resources efficiently
- Detecting safety signals early
- Minimizing revisions to key risk indicators and thresholds

CONCLUSION

The shift to using a RBM methodology requires new thinking and ways of working to execute clinical trials effectively. While it could be argued that risk management (like quality) is "everyone's responsibility," when a function is not owned by anyone in particular, it too easily falls by the wayside. People's "day jobs" have a way of consuming their time and attention, leaving none for the mutually shared responsibility. Plus, assessing and mitigating risk requires special skill sets and experience that are not necessarily to be found with the typical study team.

The answer is to give one individual—a Clinical Risk Manager—the mandate to ensure that risk management principles are applied throughout each trial. With the addition of an experienced and dedicated Clinical Risk Manager to the trial team, companies can be sure of reaping the benefits of the RBM approach.

REFERENCES

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