Risk-based Monitoring Strategies for Improved Clinical Trial Performance

To address draft regulatory guidance for risk-based clinical trial monitoring, sponsors should consider strategies that utilize social, mobile, analytics and cloud technologies to create responsive methodologies that satisfy both the spirit and letter of these new guidelines.
Executive Summary

Global regulatory agencies require sponsors to oversee their clinical trials and ensure proper monitoring of the investigation. Sponsors need both infrastructure and processes to protect the safety of their research subjects and ensure trial data integrity. In 2011, both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) released draft guidance for the conduct of risk-based monitoring to assist sponsors in better meeting their regulatory obligations.

While these guidelines provided the regulatory perspective and rationale for risk-based monitoring strategies, they did not mandate specific methodologies for implementation. The lack of an industry-based precedent regarding trial effectiveness – and the unknown impact of risk-based monitoring methodologies – pose stiff challenges for sponsors, who must implement well-articulated and documented risk-based monitoring solutions.

Traditional systems for managing clinical trials typically include a combination of software and paper-based processes intended for a variety of purposes, including project management and milestone tracking; safety/pharmacovigilance reporting and tracking; document management; trial master file maintenance; and electronic data capture and query management. In these systems, data from disparate repositories are not integrated into alerts that prompt users to take risk-mitigating action in the manner prescribed by the guidance. Information is tracked within these separate systems and made available to users through disconnected, pre-programmed status reports. The lack of technology enablers and heavy reliance on manual tracking to analyze disparate data are among the major obstacles that sponsors face as they determine how to create risk-based monitoring strategies, using only their existing infrastructure and technology assets.

A new platform is needed to accelerate the gathering and understanding of clinical trial data. Risk mitigation strategies
have little value unless they are executed, monitored and analyzed continuously throughout the trial’s lifecycle. Sponsors and their global project teams need a comprehensive and compliant solution, one that allows trial oversight through real-time proactive risk assessment. Rather than mirroring data from static repositories on a standard tracking interface or report, project teams need automated, smart logic-based workflows, alerts, escalations and audit trails to identify issues and provide consistent and traceable “actionable outcomes” to reduce risk and improve overall quality and compliance.

The availability of real-time, continuously analyzed data and configured workflows greatly reduces, or even eliminates, the potential for individual bias in issue management and decision-making. Team members are not relegated to their own — and possibly flawed — interpretations of the issues, thereby negatively impacting the compliance and quality of the study.

The key to efficiently enabling risk-based monitoring is ensuring a continuous flow of study and site data, combined with analytics, which are then monitored for trends to inform
real-time decision-making. With cloud-based and real-time access to actionable risk and performance indicators through a private infrastructure available via the Internet, global project teams would have complete visibility to critical information, analytics and associated workflows, providing clinical trial sponsors with a consistent method to evaluate, manage and mitigate risk.

This is a key differentiator from traditional clinical management and reporting systems currently in use. Having this capability allows clinical trial sponsors to focus mitigation efforts on the issues representing the greatest risk to research subjects and the study. Real-time data consolidation also helps alleviate the burden for staff members that currently rely on inadequate and inefficient manual processes to create and maintain a meaningful compliance posture.

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The current regulatory climate presents unique opportunities for leveraging technology to meet both the letter of the regulations and the intent of the recent draft guidance. This white paper explores how new technologies, proprietary software and well-articulated and documented algorithms can be integrated with existing software systems used in clinical trials to create an operational environment that enables sponsors to increase regulatory compliance and the overall efficiency of their trials.
A Brief Historical Perspective

Let’s take a moment to examine how and why we arrived here. Although some academic centers and government organizations, such as the National Institutes of Health (NIH), have conducted successful outcome studies without the use of extensive on-site monitoring, the pharmaceuticals industry has not followed this path. The industry’s long-standing practice and perception is that the gold standard for meeting regulatory monitoring obligations is frequent onsite monitoring visits, i.e., 100% source data verification (SDV) with regularly scheduled monitoring visits.

The perception of “more is better” persists even amid growing concerns that on-site monitoring practices are inadequate to ensure patient safety and data quality. Besides being labor and resource intensive, such monitoring practices are inherently reactive and retrospective in regards to error detection. Because of this, risks to subjects can be missed or responded to in an untimely manner. The lag time in responding to deviations or significant risks that occur in the trial depends, in part, on the timing of the issue in the monitoring cycle.

Note that the converse is also true; that is, a disproportionately high level of oversight can be expended for relatively low-risk situations. Interestingly, the 2009 Clinical Trials Transformation Initiative (CTTI) survey showed that while most respondents utilized centrally available data (meaning data gathered off-site) to evaluate site performance, only a small percentage typically used centralized monitoring to replace on-site visits. The FDA believes that targeted risk-based approaches that focus on the most critical data elements will result in more effective monitoring and help to overcome many of the limitations of on-site monitoring.

Draft Guidance on Risk-based Monitoring

European Medicines Agency Reflections

The EMA suggests that sponsors take a quantitative approach to the issue and ascribe numeric values to specific risks identified in the protocol (both high and low risks). When acceptable tolerance limits are surpassed, the appropriate monitoring escalation is triggered, (e.g., additional on-site visits). However, if a deviation falls within the set tolerance range, then it may be considered an “expected deviation” per the monitoring plan for the protocol.

The EMA states that tolerances/range limits should be defined early and documented in a monitoring plan. For those variables that are important to the trial objectives, the plan could include more emphasis on central monitoring, quality assurance and targeted SDV. The EMA guidance exists within the framework of the Clinical Trials Directive and accommodates a range of risk-adapted approaches that will simplify clinical trial processes.

Food and Drug Administration Perspective

The FDA draft guidance shares many of the central tenets of the EMA’s reflection paper, including the requirement for sponsors to do the following:

- Use a variety of approaches to fulfill their responsibilities related to monitoring investigator conduct and the progress of investigational drug and device exemption studies.
- Conduct a risk assessment to identify and evaluate risks critical to studying data and processes.
• Design a monitoring plan tailored to address the important and likely risks identified during the risk assessment (including remote, targeted and reduced SDV).12, 13

The guidance highlights the importance of documenting the monitoring plan after assessing the project risks and needs. It also recommends that sponsors analyze ongoing data to continuously assess and adjust the monitoring strategy.14 This is a vastly different approach from the traditional method of prospectively planning monitoring visits at regulator intervals, regardless of therapeutic area, trial phase or trial complexity.

Both the FDA and EMA encourage sponsors to adopt strategies that reflect a risk-based monitoring approach using a combination of monitoring strategies and activities. The approach should include a greater reliance on centralized monitoring, a sharp focus on critical study parameters (such as those specific to the safety and protection of human subjects) and a plan to address data integrity risks.15-18

The Way Forward
So, how do we get there from here? Industry sponsors must proactively and prospectively embrace risk-based monitoring, relying on the regulatory thinking and research presented in the guidance documents, as well as their previous experience with traditional monitoring methods. Sponsors are left to determine the appropriate strategies based on their own assessment of their operational and patient safety risks.

Sponsors entered the millennium armed with various IT systems that produce and store data in segregated silos, providing users with little useful real-time intelligence or holistic understanding relative to data that resides in other silos and repositories (see Figure 1). The result: Despite collecting tremendous amounts of data, stakeholders cannot necessarily identify unfavorable trends, potential risks or safety issues. Thus, they need a component or capability that consolidates data continuously and automatically, to fully integrate data from disparate systems and maximize their investment in existing infrastructure and technology assets.

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**Systems of Record Information Flow in a Typical Clinical Trial**

- **SAFETY/PVG**
- **TMF**
- **EDC**
- **CTMS**

**BUSINESS INTELLIGENCE LAYER NEEDED**

*Figure 1*
Given the myriad of hardware- and software-based systems, data repositories and processes that already exist, the challenge will be to integrate data streams into cohesive intelligence that enables stakeholders to make better and more timely decisions. It is critical that the chosen methodologies are transparent and that the decision process is fully documented and defined. Sponsors should be able to demonstrate that these processes are consistently followed by key stakeholders who are experienced and authorized to make these decisions.

**Social, Mobile, Analytics and Cloud**

The release of these draft regulatory guidance documents in 2011 coincided with an important juncture in the evolution of corporate IT. The next master architecture for enterprise IT is based on social, mobile, analytics and cloud technologies, or the SMAC Stack™ (see Figure 2). The constancy of these technologies in a wide array of consumer-facing markets, including the historically conservative banking industry, has laid the foundation for a new master corporate IT architecture to enter the enterprise world.9

Key to successful utilization of SMAC technologies is holistic deployment. In combination, the four components exert a multiplier effect (e.g., mobile inputs driving real-time analytics) that can serve as the foundation for breakthrough business results. In our view, the SMAC Stack will drive exponential growth in both computing devices and data. According to estimates, by 2020, up to 100 billion devices will be connected to the Web, and corporations will be managing 50 times the data that they deal with today.10 The pharma companies that will be best positioned to meet risk-based monitoring guidance, as well as conduct efficient and compliant trials, are those that can reduce reliance on on-site monitoring and maximize use of collaboration, communication and predictive analytic capabilities.

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**Catching the Fifth Wave of Corporate IT**

![Graph](image.png)

Figure 2
A critical success factor is tying SMAC technologies to key core knowledge processes; that is, putting processes rather than technology first, and then maintaining focus on the most important constituents. Technology for the sake of technology will not win the day. Pharma companies need to understand which processes are necessary and ensure that the required knowledge base is infused into those defined processes. This is very much in keeping with the philosophy of risk quantification espoused in the draft guidance documents.

The Solution: Cloud-Enabled Collaboration, Predictive Analytics

We have developed a private cloud-based, hosted performance management platform that provides efficient and active oversight of sponsor companies’ clinical trial portfolios (see Figure 3). It does this by monitoring study and site performance using collaboration and predictive analytic capabilities and enhanced communication. The platform – called SmartTrials™ – was designed to drive timely decision-making and proactive risk mitigation through improved data visibility and communication and collaboration capabilities. The solution is based on a secure, private infrastructure platform that consolidates and standardizes data to provide a fully integrated proactive performance management ecosystem. Productivity improves by leveraging automation and increasing access to information, workflows and alerts to drive improvements in quality and compliance (see Figure 4, next page).

SmartTrials: A High-Level View
Key Risk Indicators and Scoring

To address the adoption of risk-based monitoring methodologies, we have developed a proprietary risk assessment scoring tool that provides consistent scoring for key risk indicators (KRIs) at the investigative site level. The resultant weighted scores drive the monitoring strategy and can be reassessed throughout the monitoring cycle.

The KRI scoring tool is used to measure the impact of threshold breaches across combinations of several KRIs, simultaneously, as the study progresses.

The KRI scoring tool is used to measure the impact of threshold breaches across combinations of several KRIs, simultaneously, as the study progresses. This risk-based monitoring methodology allows for documentation of issues and risks, as well as decisions made and actions taken in response to those risks, in keeping with both EMA and FDA expectations. With full audit trails, sponsors can demonstrate to regulators that patient safety and data integrity remained the overarching priorities throughout the conduct of the trial, both fundamentally and quantitatively. Risk-scoring data from completed trials can be used to evaluate acceptability of sites for future studies.
Social Networking Functionality

SmartTrials leverages the principles of social networking, using a powerful information platform to streamline communications and provide a central access point for teams to communicate, share information, collaborate and stay connected in a secure role-based environment. Portals for executives, management, program teams, contract research organizations (CROs) and investigators provide an end-to-end means for sharing important information, ideas, best practices, successes and lessons learned. The ability to collaborate securely across organizations and global project teams, both internally and externally, promotes team engagement and improved productivity.

Analytics Capability

SmartTrials’ analytics framework provides visibility into best-in-class performance dashboards, using metrics, key performance indicators (KPIs), key risk indicators (KRIs) and risk-based assessment scores with near-real-time data access. Data capture is automated, eliminating the need for the project team to manually collect and consolidate data on an individual basis.

Each data point can be utilized in different ways. First, users can drill down and review individual data points and values. Then, data can be consolidated using algorithms and configurable thresholds to drive alerts, escalations and action items to project teams. Finally, complex data analysis provides users with a 360-degree view of issues that are highlighted by SmartTrials’ to drive risk mitigation activity, improve quality and ensure overall program compliance.

A Smarter Way to Conduct Clinical Trials

Figure 4
Integration with Existing Systems

Data accelerators are pre-built with standardized implementation plans and integrate with clients’ clinical trial management (CTMS), electronic data capture (EDC) and document management systems, as well as other third-party software, resulting in a shorter timeline to full platform usage. SmartTrials can integrate with an unlimited type and number of systems and platforms. Integration can be achieved in multiple ways, based on sponsor requirements and operating environment.

The cloud-based architecture, accessed through a private infrastructure, simplifies user access and requires only an Internet connection. The solution allows trial stakeholders, whether at the sponsor or CRO (or other vendor), to access data in context with other existing data silos and repositories used to support the trial. Disparate data are reflected, in context, through an accessible user interface, delivering meaningful intelligence that drives rapid trend identification, proactive decisions and shorter response time.

As noted in our earlier SMAC white paper, “The SMAC Stack does not represent the next new technology to be bolted onto your existing business model. Instead, these technologies will transform the business model, itself.” (See “Don't Get SMACked: How Social, Mobile, Analytics and Cloud Technologies Are Reshaping the Enterprise.”) SmartTrials integrates SMAC functionality throughout the solution, at every layer of the platform (see Figure 4). This includes:

- **User access**: Web-based and intuitive user interfaces simplify access, training, deployment and adoption.
- **Portals**: Sponsor executives and program teams, CROs and investigators can access an end-to-end platform for collaboration and business process management.
- **Collaboration**: Workflow solutions utilize social networking tools that enable users to connect with their colleagues in multiple ways and provide users with an integrated platform for sharing information, news, ideas, best practices, successes and lessons learned in an easy-to-use and engaging platform.
- **Business process management**: A framework that delivers predictive analytics and uses operational performance metrics, key risk indicators, algorithms, risk scoring and thresholds, with near-real-time access to data to better manage business performance by enabling efficient decision-making at all levels.
- **Integration**: A standardized integration framework, coupled with prebuilt integration accelerators, enables rapid deployment.

In addition to private cloud-based access via the Internet in traditional office settings and home offices, our SmartTrials solution can also be accessed through mobile devices, allowing even greater flexibility for project team members who need mobile access to project information.

Conclusion

New strategies for existing technologies will be needed to achieve global risk-based monitoring. The convergence of risk-based monitoring methodologies with the continued immersion of social, mobile, analytics and cloud-based technologies throughout global markets presents both challenges and opportunities for the way clinical research is currently conducted.

Sponsor companies (or their vendors) that can leverage SMAC against existing infrastructure and technology assets will best position themselves to meet new
regulatory guidance and adopt monitoring practices that are practical, purposeful and flexible enough to ensure proper oversight throughout the clinical trial lifecycle.

The advent of merging SMAC technologies with risk-based monitoring does not diminish opportunities for growth. The adage of “doing more with less” comes to mind in the context of a waning R&D pipeline and expiring patents. Even with this backdrop, 2013 presents tremendous opportunities in terms of total spend, numbers of studies, location/distribution of sites and drivers for innovation, especially to leverage technology in an integrated and comprehensive way to meet regulatory challenges.

Conforming with a single risk-based monitoring methodology would be nearly impossible if it meant abandoning current practices and divorcing infrastructure assets.

In 2012, member companies of the Pharmaceutical Research and Manufacturers of America (PhRMA) – which includes both global and U.S.-based companies – invested an estimated $48.5 billion in R&D, with more than half a trillion dollars in R&D investments since 2000. There are still more than 5,000 medicines in clinical trials globally or under FDA review, with almost 60,000 interventional clinical trials registered in the U.S., alone.

One Size Does Not Fit All

It would be impractical for a regulatory agency to mandate a one-size-fits-all approach for the implementation of a risk-based monitoring solution. Although a challenging frontier, the open-ended framework of the draft guidance allows sponsors to customize a solution that works best for their individual profile. With their rich history of paper-based documentation and manual processes, companies entered the millennium with their own unique infrastructures and technology profiles. Conforming with a single risk-based monitoring methodology would be nearly impossible if it meant abandoning current practices and divorcing infrastructure assets.

Pharma companies that conduct clinical research in the most efficient and compliant manner will maximize the return on their decades-long infrastructure and technology investments and position themselves to make valid determinations about advancing a particular drug or treatment program through the development pipeline.

Regardless of therapeutic area or scale of clinical trial, sponsors must embrace and adopt the tenets of risk-based monitoring in the context of the prevailing global IT architecture. This will enable them to meet the regulatory requirements pertaining to the protection of research subjects and deliver focused and accurate supporting data to regulators. Sponsors that do this will also propel their existing technology assets into a framework for responsive, compliant, accurate and intelligent clinical trial design and conduct.
Footnotes

1. 21 CFR Part 312.50
2. 21 CFR Part 812.40
7. Ibid.
15. Ibid.
20. Ibid.
21. Ibid.
22. Ibid.
27. ClinicalTrials.gov.
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