The Foundation of Risk-Based Monitoring Success

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Clinical Monitoring Leaps Forward

Considering the ever-rising cost, scope and complexity of clinical development, life science companies, contract research organizations (CROs), regulatory agencies and industry organizations are striving to find cost-effective ways of conducting on-site monitoring as this is the most costly aspect of running clinical trials.[1]

The most significant approach to emerge in the last decade for a more efficient, cost-saving way to improve clinical trial monitoring is risk-based monitoring (RBM). This approach has been widely encouraged by regulatory agencies and is gathering momentum in adoption by sponsors and CROs. Proponents of RBM projects believe that the investment in this approach will return an overall reduction in monitoring expense by 15 to 20 percent.[1] This paper discusses RBM as a high-value use case that can be enhanced by a robust clinical data aggregation and analytics solution.

Standard Monitoring Practices

For many years, most approaches to clinical trial monitoring have relied heavily on 100 percent source document verification (SDV) and other on-site monitoring functions to ensure the safety of study participants and the integrity of study data. However, SDV is a very time and resource intensive practice, requiring clinical research associates (CRAs) to check every data point on the information reported by investigators against source records to ensure data accuracy and validity. In addition, SDV is applied uniformly throughout a trial rather than proportionate to the risks.

It has become evident that this costly practice has had a negligible impact on data quality. In fact, according to a position paper on RBM by TransCelerate, an industry organization composed of leading global biopharmaceutical organizations, only 2.4 percent of all data queries generated from nine of its member company studies were SDV-related. The results support TransCelerate's recommendation to shift from on-site monitoring to a risk-driven, tailored approach.[2]

RBM calls for targeted monitoring to reduce the amount of SDV, based on risk assessment to identify core critical data supporting trial endpoints and patient safety. The extent of monitoring vacillates based on key risk indicators (KRIs) and data trends during the trial. Following a risk assessment, resources are allocated across a study based on data criticality, patient safety, data integrity, protocol compliance, and the impact to operational delivery.

For effective RBM, the first fundamental step is full integration of the vast amounts of data coming from many different sources and systems, which must take place before data analysis can begin.

Fundamental Clinical Operations Challenges

At the end of the day, program, country and study managers must be able to model and set trial budgets based on fixed and variable budget components and achieve trial milestones. Unfortunately, information on budgets and milestones is typically not readily available and easily accessible. With nearly 80 percent of clinical trials failing to meet enrollment timelines[3] and significant delays across many programs, proper oversight of clinical development operations is imperative. Clinical operations managers and CRAs struggle with visibility into trial progression at global sites, issue detection, and slow, cumbersome reporting methods.

The top five drivers of cost leading to trial budget increases are protocol amendments, timeline delays, increasing number of participating sites, changes in monitoring strategy, and vendor misalliances causing changes in vendors mid-study.[4]

Unanticipated events occur throughout the trial, such as delays in recruitment of sites and subjects. In fact, more than 80 percent of clinical trials experience delays ranging from one to six months, costing companies upwards of $35,000 per day, per trial. Only 10 percent are completed on time.[5] A typical Phase III clinical trial takes nine months to complete enrollment and can cost up to $86 million. The cost of initiating a site ranges from $20,000 to $30,000, maintaining sites is estimated to be about $1,500 per month, and 11 percent of sites in a given trial do not enroll a single patient.[6]

More data sources than ever before contribute to the clinical trial budget, creating complex, time-consuming and multifaceted financial management. With the increase of outsourcing, data from multiple vendors and contracts end up in disparate systems, and the lack of integration prevents the data from being easily used for accurate, efficient financial management. Data from multiple systems must be pulled and analyzed in cumbersome Excel worksheets.

Unfortunately, part of the investment in clinical trial data collection is wasted. From 2006 to 2010, the global pharmaceutical industry wasted nearly $2 billion on site start-up costs as a result of non-performing sites, and between 2008 and 2011, per-patient clinical trial costs rose an alarming 70 percent, with 46 percent of the increase attributed to patient enrollment. Under-performing sites resulted in budget overruns.[7] In addition, up to 30 percent of the data collected by industry sponsors (estimated to cost $1 million) is never used in an FDA application, and 25 percent of all procedures are not associated with any of the key endpoints.[8]

In a Phase II oncology study with a budget of approximately $10 million, completed in 420 days, the actual study cost compared to study budget was $1.1 million more than planned. According to an industry survey, this represents a typical scenario for nearly half (45 percent) of the life sciences professionals who reported that their typical variance from forecast to actual costs for clinical studies was at least 11 percent. And an astonishing one in five stated their cost variance was 16 percent or more.[9]

Outsourcing

Sponsors are expanding their outsourcing of clinical trials to CROs and other service providers and downsizing their IT staff in favor of leveraging SaaS-based vendors. According to a Nice Insight survey, sponsors have increased their outsourcing of clinical trials from 20 percent in 2012 to 41 percent in 2014.[10] Analysts estimate clinical research outsourced to CROs will grow to a projected $60.8 billion by 2016.[11]

Given the recent ICH GCP E6 R2 guidance, total responsibility of trial oversight, including CRO outsourced trials, are now the sole responsibility of the Sponsor. While a good first step, outsourcing only cuts costs and drives efficiency so much. The burden then gets shifted to the CROs who are starting to turn to RBM as a solution to streamline their internal operations and cut their costs.

How RBM Is Effectively Implemented

At the beginning, a risk-based monitoring road map must be put in place. The RBM working group as part of the Metrics Champion Consortium (MCC) defines the process to get agreement on the definition of the mapping between risk signals and monitoring activities as follows:

- Agreeing on a common terminology
- Defining success criteria
- Creating an RBM process map
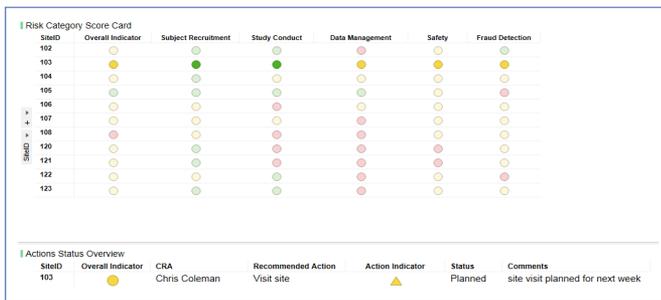- Defining and categorizing site risk signals

Figure 1. Category-level risk indicators by site. Sites can be selected to view the KRI roll-up to category and overall levels.
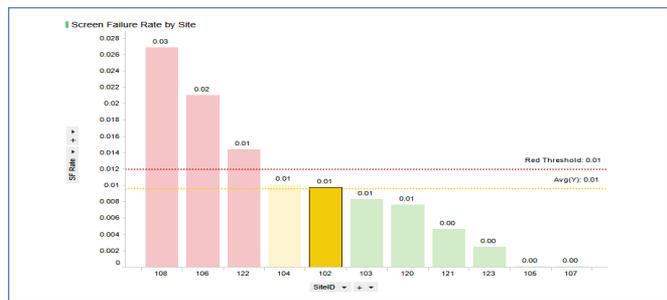

Figure 2. Screen failure ratio by site, adjusted for months in study.

This is dependent on upper management support to build RBM into protocol designs and propagate this new methodology throughout the organization to gain acceptance and alignment.

With this in place, more centralized off-site monitoring with minimal on-site visits, and an integrated quality and risk management plan can be tailored to each trial. From a technology standpoint, the solution must be powered by technology that fully integrates the vast amount of data coming in from multiple sources in silos as risk-based monitoring of clinical trials requires the integration of disparate data sources and formats as well as relevant analytics to enable rapid identification of outliers and trends in large volumes of data.[2]

The solution must leverage flexible technology to process and aggregate the data. The technology must be flexible enough to load data from any application, database, line listing, file or report. Users must be able to learn from previous mappings to reduce manual work as use of the system expands. Patient data in the CDISC SDTM (study data tabulation model) format and clinical operations data into ODM (operational data model) format must be compatible. Full data integration is needed to drive platform agnostic dashboards and analytics.

Risk Management

The Risk Assessment and Categorization Tool (RACT) was originally developed by TransCelerate to identify and assess risks, which in alignment with critical data/processes, direct the level of intervention when monitoring sites. KRIs, therapeutic and study-specific risk templates, and mitigation steps are then integrated. The RACT was designed to identify how and by which functions the risks will be managed; document risk mitigations; categorize individual risks as high, medium, or low; and provide guidance to determine the baseline of monitoring activities, including suggestions for SDV.

After defining critical data and processes, study-specific key risk indicators (KRIs) are created and defined, with thresholds designed to trigger an action, such as increased data scrutiny. Alerts can be delivered by email or text with a link in the system to the issue as thresholds are reached based on KRIs such as: safety, investigational product, recruitment, discontinuation, issue management, data quality, on-site workload, essential documents, staffing, facilities and supplies.

Custom KRIs can be created based on the study or therapeutic area or geographic requirements of the study, and end users should be able to adjust the risk weighting throughout the study. For example, since enrollment is less important in later stages of the study, it should have a low risk weight at that stage.

KRIs, associated thresholds, and actions are documented in an integrated quality and risk management plan (IQRMP).

Advanced technology with powerful visualization capabilities enables study teams to efficiently incorporate KRIs into the study management process. The RBM system should also have an oversight risk score dashboard, show KRI weight controls, include historical risk score trends, and display risk score compared to monitoring rates.

And, an effective RBM solution should be part of a closed-loop Quality by Design (QbD) approach that supports adaptive monitoring through action and feedback mechanisms that capture historic site performance data for future site selection decisions.

Most importantly, the tool should be embedded into an overall clinical operations tracking and analytics strategy to ensure seamless interaction and decision-flow between other operational functions such as resource planning, trial portfolio management, budget planning, QbD, as well as safety and outcomes monitoring environments. Recently, a number of niche vendor solutions have entered the market that are disconnected from existing decision support systems in clinical operations, which prevent the most positive gain on trial efficiency.

Conclusion

As RBM evolves, we are seeing that in order to effectively implement RBM, there are ties to other business functions within an organization that need to be aligned as well as upper management support and acceptance of RBM within the clinical operations ranks. From a baseline technology perspective, solid data integration and analytics are at the foundation of any successful RBM solution.

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