Risk-based monitoring has attracted the support of a diverse group of organisations in recent years. Regulators have released guidance encouraging the use of risk-based approaches to clinical trial quality, vendors have created technologies to support such methods, and large pharma companies have pooled their resources to drive adoption. Yet, despite this flurry of activity, the industry has overlooked a potentially useful source of real-time and historical data.
SMARter, DATA-DRIVEN MONITORING

THE FDA SEES RISK-BASED MONITORING AS A FACILITATOR OF CONTINUAL IMPROVEMENT IN HOW TRIALS ARE RUN AND OVERSEEN

In essence, risk-based monitoring is a way for sponsors and CROs to focus their time and resources on the trial activities, data, and sites most critical to the success of the trial and safety of the patients. Instead of treating each site the same, organisations using a risk-based approach can tailor their approach. Communication with clinical investigators, reviews of study centres’ processes, procedures, and records, and Source Data Verification (SDV) activities can be adapted to each site’s past and current performance. The idea is to raise the quality of clinical trials not by doing more monitoring, but by doing smarter, more data-driven monitoring.

Historically there were doubts about the FDA’s openness to the approach, but guidance has clarified the situation. “A risk-based approach to monitoring does not suggest any less vigilance in oversight of clinical investigations,” the agency wrote in its guidance on the topic. “Rather, it focuses sponsor oversight activities on preventing or mitigating important and likely risks to data quality and to processes critical-to-human-subject protection and trial integrity.”¹ The FDA also sees risk-based monitoring as a facilitator of continual improvement in how trials are run and overseen.

With the FDA and the European Medicines Agency in favour of risk-based monitoring and sponsors and CROs keen to improve trial quality while controlling costs, the model has attracted considerable interest in recent years. Monitoring can account for upward of 30 percent of clinical trial budgets, creating considerable scope to drive down costs through better use of resources. Metrics on how many companies have embraced risk-based approaches are limited, but those available suggest the concept is going mainstream.

In 2013, Metrics Champion Consortium found 55 percent of the 38 North American drug developers and CROs it polled were already using risk-based monitoring. While many of the companies may have only been deploying risk-based monitoring in pilot projects, the survey still shows widespread interest in moving away from 100 percent SDV — the practice of checking all data against medical records and other source documents and data — and toward the use of remote, risk-based clinical trial oversight and central data analytics.

For such targeted, off-site monitoring to work, sponsors and CROs need access to data. Historical data informs the selection and development of risk indicators and accompanying thresholds. For example, if precedents show query responses should be added to case report forms within five days, a study may set “query response input” as a risk indicator and “five days” as a threshold. Then, by pulling in data from the active clinical trial, a remote monitoring team can see when a study site is falling behind on entering query responses. This leads to targeted support for the site that needs help with query responses.
Sponsors and CROs use data from Electronic Data Capture (EDC) platforms, Clinical Trial Management Systems (CTMS), Quality Management Systems (QMS), and other technologies to tell when their risk indicators have passed a threshold. Timeliness is vital to this process. Remote monitoring teams need real-time data so they learn of problems as they arise and can stop them before they escalate.

Yet, there is often a lag between a site collecting data on paper or an Electronic Health Record (EHR) and entering them in an EDC platform, resulting in a cornerstone of risk-based monitoring delivering delayed data.

HOW CAN IRT DATA FACILITATE RISK-BASED MONITORING?

Sponsors and CROs have partly mitigated the weaknesses of individual data sources by designing systems that pull in information from multiple technologies, such as EDC, CTMS, and QMS. However, these systems still rely on adverse event-based risk indicators and thresholds to alert study teams to potential problems with the clinical trial. These risk indicators are affected by the aforementioned lag in EDC entries, and their usefulness is detrimentally affected by the diversity of causes of adverse events. The fact that adverse events are high does not necessarily show a clinical trial has a problem.

In light of these shortcomings, there may be value in adding Interactive Response Technologies (IRT) to the list of technologies from which risk-based monitoring systems draw data. IRTs are software programs that support the screening and randomisation of trial subjects, clinical supply management and dispensing of study drugs, and clinical supply reconciliation and accountability.
As trial sites need to use IRT to figure out which subject will receive which medication, the technology collects and shares data in something approaching real time. Sponsors and CROs can rely on data to pass from the site to their risk-based monitoring systems in a shorter period of time than is achieved by EDC, enabling them to make timely interventions.

IRT also gives study teams a way to look closely at what is happening at a trial site. While a spike in adverse events at a site is not necessarily indicative of poor practices by the clinical investigator and their colleagues, some of the metrics tracked by IRT do offer a window into their performance.

If a trial site is frequently reporting on-site temperature excursions, it suggests the staff needs help managing the cold chain. Sponsors and CROs can offer such support once the “quarantine” risk indicator passes a preset threshold. IRT data can also show study teams when unusually high numbers of resupply visits occur outside the preferred time windows at a site. Like the excursion data, the visit information gives study teams a near-real-time look at a metric that correlates to the competency of a site.
To implement such IRT-based risk indicators, sponsors and CROs must analyse historical data to learn the appropriate thresholds for the visit performance, discovery of late shipments, temperature excursions, dispensing errors, and other metrics the risk-based monitoring system will track. This analysis can also reveal data that can inform the design of the trial or the clinical supply packaging and distribution strategies. If, for example, the number of dispensing errors is seen as a correlate of site quality, the study team can use historical IRT data to show which centres have a track record of performing well against this metric and enlist them to join the clinical trial.

Applied effectively, IRT-based risk indicators could enable study teams to augment their risk-based monitoring strategy with additional proactive metrics to monitor clinical trial integrity and site performance. Instead of waiting for an uptick in adverse events to suggest a site is struggling to manage aspects of a clinical trial, the study team could use IRT data to inform targeted, risk-based interventions before the problems on the ground affect patient safety. This fits squarely with the FDA’s description of risk-based monitoring as a way to focus “sponsor oversight activities on preventing or mitigating important and likely risks … critical to human subject protection.”

IRT-BASED RISK INDICATORS

STUDY TEAMS COULD USE IRT DATA TO INFORM TARGETED, RISK-BASED INTERVENTIONS BEFORE THE PROBLEMS ON THE GROUND AFFECT PATIENT SAFETY
Today, IRT is a largely, perhaps wholly, untapped source of risk-based monitoring data. TransCelerate BioPharma, a consortium of large biopharma companies that has released guides to encourage the adoption of risk-based monitoring, includes IRT on the list of technologies sponsors and CRO should integrate into their data sourcing systems. Yet, despite having the validation that comes with the support of TransCelerate, IRT is yet to join EDC as one of the cornerstones of risk-based monitoring systems.

This may reflect the relatively low profile of IRT and a wider unfamiliarity with what the technology does. Whatever the reason, the slow incorporation of IRT data in risk-based monitoring strategies represents an opportunity for sponsors and CROs, both in terms of planning upcoming trials and overseeing their progress.

On the design front, with the Tufts Center for the Study of Drug Development calculating 11 percent of sites fail to recruit a single patient and a further 37 percent fall short of targets, there is a need for data that supports predictions about the competencies of research centres. IRT data can suggest which sites are best equipped to run clinical trials, resulting in the sponsor activating fewer ineffective centres that take up a disproportionate amount of the study team’s time. Once the trial is running, study teams can use the near-real-time data provided by IRT to proactively manage quality.
INVESTING IN THE RIGHT IRT WILL CONTINUE TO PAY DIVIDENDS FOR YEARS TO COME

These opportunities are available to sponsors and CROs today. The data is already being collected by sites and internal and external pressures to raise quality while maintaining costs are unlikely to lessen. As such, investments to build the information into risk-based monitoring systems should continue to pay dividends for years to come.

GET IN TOUCH

UK
Almac Group
(Global Headquarters)
Seagoe Industrial Estate
Craigavon
BT63 5UA
United Kingdom
clinicaltech@almacgroup.com
+44 28 3835 2121

US
Almac Group
(US Headquarters)
25 Fretz Road
Souderton, PA 18964
United States of America
clinicaltech@almacgroup.com
+1 215 660 8500

ASIA PACIFIC
Almac Pharmaceutical Services Pte. Ltd.
(Asia Pacific Headquarters)
9 Changi South Street 3
#01-01
Singapore 486361
clinicaltech@almacgroup.com
+65 6309 0720

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