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Watch and Wait

With 100% source data verification looking ever-more out of date, the large-scale adoption of risk-based monitoring is only a matter of time. But this more centralised, proactive method of data analytics requires a full quality management cycle to ensure industry realises its true value

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The effective monitoring of clinical trials during the development of new medicines is critical for the protection of subjects and patients, and for ensuring that sponsor companies get high-quality data for submission to regulatory authorities. At the same time, monitoring is the single-largest cost factor of clinical studies, typically comprising 25-30% of all trial costs.

Most monitoring activities focus on 100% source data verification (SDV), but this percentage could be reduced with no effect on overall data quality. The main drawback with 100% SDV is that it cannot guarantee subject safety because the process only detects data quality issues after the clinical trial has taken place. Also, there is little evidence that conducting 100% SDV has any significant impact on data quality or enhances regulatory trust in the data. On the other hand, it may actually delay study completion and not make best use of investigational site resources.

As a result, R&D-based pharmaceutical companies are increasingly looking to adopt a risk-based approach to their monitoring activities by applying statistical analysis and control to investigate site data – thereby reducing reliance on SDV.

The UK's Medicines and Healthcare Products Regulatory Agency, the FDA in the US and the European Medicines Agency first issued draft guidance for risk-based monitoring (RBM) for clinical studies in August 2011. This outlined how the application of RBM could result in considerable cost and time savings for sponsors, while also enhancing patient safety by leveraging technologies such as big data analytics (1-3).

RBM Promise

Using a risk-based approach, and monitoring changes proactively rather than reactively, can help guarantee subject safety and improve data quality through early identification or even prevention of issues. Sponsors can allocate greater resources – including clinical research associates and time – to higher risk sites, thereby optimising costs and improving the quality of data. As such, the large-scale adoption of RBM across the industry holds the promise of bringing innovative medicines to market faster, at a lower cost and without compromising on quality.

For the successful implementation of RBM, there are a number of factors to consider:

Approach

Firstly, sponsor companies need to define the extent to which they will implement RBM – will it be for all therapeutic areas, projects and studies? The monitoring approach then needs to be tailored to the individual study protocol.

Processes

Significant upfront work is required to develop or modify existing processes for risk and quality management for the monitoring of clinical studies. This includes updates to standard operating procedures (SOPs) and working instructions.

The application of RBM requires sponsors to identify which data is critical at both the overall compound level for the drug being investigated, and for the individual clinical study protocol. Sponsors also need to determine acceptable quality levels and establish mitigation plans to be enacted if the data falls outside these set boundaries. Once this has been established, metrics are used to ensure continuous monitoring of critical data quality. The degree of monitoring activities for a particular study protocol is described in the monitoring plan. Sponsors should brace themselves for an initial spike in the complexity of study planning and operations.

Organisation

It is vital that the risk and quality management disciplines are made part of the programme/project/study processes in which technicians are trained. Under RBM, monitoring is no longer restricted to the mere checking of data; it will instead move to a full quality management cycle of 'plan, do, check and act'.

The biostatistician will need to perform different types of analytics beyond what had previously been foreseen. Therefore, sponsors cannot expect their existing technicians to have the necessary skill set to differentiate between critical and non-critical data. Strong collaboration and communication between sponsor and sites is essential throughout – this can be made easier with the use of study-specific micro-sites.

Infrastructure

Technology has a significant role to play. The collection, cleansing, consolidation, analysis and real-time reporting of large quantities of data is made possible by the widespread adoption of electronic data capture and other systems that collect clinical study data online and in real-time. This data needs to be overlaid with advanced analytics capabilities and intuitive reporting that can raise red flags in the data and study management systems if the dataset falls outside defined ranges, triggering intervention in such cases.

Over a period of time, sponsors can identify the key performance indicators (KPIs) that prove most predictive and effective in identifying sites at risk. They should then build a knowledge base of these KPIs for potential reuse across broadly similar projects and studies. This can be hosted on a cloud-based infrastructure to provide global, cost-effective analytics access to both sponsor companies and investigational sites.

Location

Finally, monitoring will need an on-shore/on-site capability. However, just as the transactional components of data management processes are conducted off-site and are offshored, a large chunk of the risk-based central analytics activities can be located anywhere in a dedicated and cost-effective centre. This will require much of the same configuration of competency centre operating models, establishment of processes, SOPs and service-level agreements, as well as appropriate project management and communication tools.

Forward Momentum

As the regulatory agencies have only recommended the RBM approach without making it a binding policy, pharma companies can use their discretion to implement it. However, the industry will surely adopt the new model in accordance with the guidelines before long, thanks to the continued advances in technology in the form of digitisation, and the standardisation of clinical study data and advanced analytics. Centralised and offshored monitoring looks set to bring about significant time and cost savings, while also ensuring better data quality and greater patient safety.

References

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3. Transcelerate Position Paper: Risk-based monitoring methodology. Visit: www.transceleratebiopharmainc.org/sites/default/files/uploaded-files/risk-based%20monitoring%20methodology%20position%20paper_0.pdf

About the author

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