Statistically Speaking -

Why a Hybrid of Centralised Statistical Monitoring and Key Risk Indicators could be the Answer for Risk-based Monitoring

The industry is at a crossroads when it comes to data-driven monitoring practices in clinical trials. While traditional approaches still dominate, new methodologies are increasingly implemented that facilitate more efficient trial delivery and hold the potential to further reduce risk, while improving patient safety and data quality.[1] Until recently, risk-based monitoring (RBM) systems have relied widely on the use of key risk indicators (KRIs) to identify anomalies in data and deviations in study conduct, and to allow research sponsors to identify performance issues at investigative sites. KRIs are defined by the British Medicines and Healthcare Products Regulatory Agency as:[2]

- Recruitment rates
- Screen failure rates
- Case report form completion time following visits
- Query rates
- Time to query resolution and number of active queries
- Serious adverse events
- Number of missed or late visits
- Number of participant withdrawals or drop-outs
- Number of protocol/GCP non-compliances

Subjective by nature, this approach has proven limited insofar as it uses only part of the data collected in a clinical trial. The threshold value that triggers a KRI is also typically an arbitrary value that may vary from trial to trial, from region to region, and over the course of a trial's lifecycle. Irrespective of this, KRIs remain a critical aspect of RBM. To enhance the detection of anomalies in clinical trials, a hybrid methodology that brings together KRIs with the unique aspects of central statistical monitoring (CSM) could hold the answer. Here we look at how the use of CSM techniques in conjunction with KRIs can enhance monitoring strategies, and outline a pragmatic workflow that may help sponsors better mitigate risk by quickly identifying and responding to signals and trends that could impact study performance.

The CSM Approach

KRI-based RBM methodologies can be considered "top down" because study personnel define and then test the KRIs against the data to identify potential issues. By comparison, CSM can be considered "bottom up", because it uses the data themselves – potentially all clinical and administrative data – to identify possible issues. As a result, CSM can detect unanticipated problems in unexpected places and help target monitoring activities.

As an agnostic RBM approach, CSM uses statistical methodology to identify unexpected or unusual patterns in clinical trial databases. As all sites participating in a study will have the same case report form (CRF), the data structure is similar for all sites, making it possible to compare one site against all other sites. By using statistical modelling to drill down into individual patient data and comparing the distribution of all variables, it is able to determine the quality, accuracy and integrity of clinical trial data, both during and after a clinical study, in order to identify any abnormalities. Its comprehensive nature minimises the chance that a study might have to be repeated due to a systematic problem that is detected too late.

All data that are collected within a study are important, and there is no reason why they should not be used to monitor performance. While primary outcome variables are typically scrutinised for errors or omissions, secondary variables receive less attention and may be more indicative of problems at a site. Even patterns in other (non-primary, non-secondary) data might be important. For example, unusual lab values on blood collected on Thursdays at a particular site might reveal that the person who packages samples on that day requires further training.

Anomalies in structured datasets are easily detectable, especially by multivariate and longitudinal statistical analysis.[3-5] In a CSM-based system, clinical data can be grouped, for example, by CRF section, then by visits, then by participant, then by study coordinator, then by site, and then by country.[6] Administrative data can be similarly grouped. Data are also categorised by study arm – baseline and administrative variables should not differ between the randomised groups, while outcome variables within an arm should show comparable differences at all sites. For example, if the participants at a site have broken the blind based on the taste of the study drug vs. placebo, the placebo group might start missing more visits.

CSM-based systems perform numerous statistical tests at all levels on properties of the dataset, including means, variances, incidence of outliers, event counts, distribution of categorical variables, missing values, variation over days of the week, multivariate correlations, and so on.[6,8] From these tests, a high-dimensional matrix of p-values can be generated to identify outlying sites and specific data to monitor.[5] By doing this, they supplement standard data management and biostatistics tools for oversight of the quality of the data collected, and can also help identify the best sites for future trials. They can even identify issues in sponsor and CRO performance.

CSM emphasises the use of statistical analysis to drive the monitoring process, and while KRI-based systems can

also employ centralised statistical measurements, they are limited to pre-defined KRIs and pre-set threshold values. CSM-based systems let the dataset speak for itself.[9-11] However, what is not widely recognised is that KRI- and CSM-based methods of RBM are complementary and the choice does not need to be made between them. They can be used together in a hybrid approach to yield the best results. Table 1 compares the two methods:

Table 1. Comparison of KRI- and CSM-based RBM

	Key Risk Indicators	Central Statistical Monitoring
Method	Looks at risk factors known to be important	Looks for statistical anomalies in all data
Typical number of variables	<25 variables	>250 variables
Checks	KRI value exceeds pre-specified threshold at a site	A site shows an anomalous value or pattern of values compared to other sites
Limitations	Detects only anticipated problems; thresholds may be miscalibrated; requires human judgment and study-specific programming; requires manual recalibration during the course of a study	Can detect anomalies that are not consequential; needs substantial data to function; cannot analyse data that are not computerised (e.g., hand-written notes and interviews); complex statistical analysis may be opaque

Most anomalous data are due to unintentional causes, such as ambiguity in the protocol, lack of training, or simple error. KRI-based systems will detect such issues, provided they trigger one of the defined variables in a study. Used in conjunction, CSM-based systems will detect a much more comprehensive range of anomalies without any pre-programming. Putting together a workflow that achieves the most appropriate approach for a particular study is critical in creating a successful and cost-effective monitoring strategy.

A Pragmatic Workflow

A well-defined workflow for RBM is fundamental to directing the right resources throughout the course of a clinical trial. Incorporating a CSM solution with an integrated KRI approach offers huge potential.

Risk-assessment Categorisation

In combination, CSM and KRI approaches can assist with detecting threats to data quality. However, this is not a one-size-fits-all approach. The methodology put into practice for any study will differ based on the protocol. As a result, risk-assessment categorisation is playing a considerable role in determining the upfront risk to a planned trial, and informing the monitoring methodology. As recommended by TransCelerate's guidance paper, the creation of an integrated, multifaceted approach to proactively detect data quality issues is necessary, and detection methods should include a strategy tailored to the characteristics of the study.[12]

By utilising a risk assessment categorisation tool (RACT) within a CSM platform, sponsors can establish an operational workflow that ensures a comprehensive risk mitigation plan, using the appropriate KRIs to tailor data analyses based on the specific risks associated to a study. By allowing sponsors to navigate into various categories and answer questions in terms of impact, probability and detectability of various factors in line with the TransCelerate methodology, these tools provide an intuitive workbench to identify, interpret and document study risk factors.

KRIs

Once appropriate KRIs have been defined (derived from both operational and clinical data), sponsors are able to implement their own triggers for action across key operational variables. A KRI approach that is underpinned by the use of statistics gives a much more objective approach than the subjective thresholds and trigger levels. Frequent operational analysis can be conducted continuously, although in most cases it will be done every two to three weeks.

Targeted Data Quality Assessment

Targeted data quality assessment should be undertaken every four to six weeks to pinpoint potential quality aspects that really matter within clinical and operational data. Using powerful statistical analysis, sponsors are also able to determine future KRIs based on the output, and identify discrepancies that are observed. New CSM technologies allow sponsors to select critical domains within a study, such as safety data or primary/secondary endpoints, with a view to analysing only these data that matter. These systems analyse every variable pertaining to the critical elements and surface all significant anomalies across sites. The resulting visualisation of results enables clinical operations staff or data managers to easily drill down into outliers and determine the corrective action necessary. This methodology provides a more comprehensive analysis of important data that is still easily interpretable by stakeholders to find and remediate errant data and other anomalies.

Overall Data Quality Assessment and Quality Stamp

Undertaken every two to six months, overall data quality assessment identifies atypical centres, countries, regions and patients. All data are comprehensively analysed to achieve a quality stamp on submitted data. This ensures that regulatory authority submissions are of appropriate quality and provides sponsors with the ultimate risk mitigation tool. This rigorous interrogation of all clinical data is more sophisticated than using KRIs alone and allows users a complete assessment of the quality and integrity of data. Already recommended by regulatory authorities, overall data quality assessment risk mitigation tools can be used by data managers and biostatisticians to detect anything, including unintentional errors (miscalibrated equipment), propagation of data, site training issues, misunderstanding of protocols and, ultimately, fraud.

Conclusion

Risk-based monitoring that delivers clearly documented upfront and ongoing risk assessment in clinical trials is transforming clinical development. Independently,

CSM- and KRI-based approaches both demonstrate benefits in helping sponsors meet regulatory guidelines and improving study success rates. However, tailoring a hybrid of these methodologies for a study's monitoring strategy, and implementing a workflow that delivers the most comprehensive analysis of data, allows sponsors to quickly identify and respond to potential issues, offering huge potential to the industry in simultaneously driving patient safety and data quality.

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