JOURNAL OF CLINICAL RESEARCH BEST PRACTICES

Vol. 10, No. 11, November 2014 "Happy Trials to You"

A Statistical Approach to Risk-Based Monitoring

By Marc Buyse

Most risk-based monitoring (RBM) systems rely largely on Key Risk Indicators (KRI) to reveal deviations in study conduct and identify performance issues at specific research sites in a clinical trial.[1] With this approach to RBM, pre-defined KRI metrics are measured for each site to determine on-site monitoring frequency and scope. The British Medicines and Healthcare Products Regulatory Agency has posted a list of KRIs on its website, including the following:[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

TransCelerate's position paper on RBM methodology offers guidance on the use of KRIs.[3] KRIs are an essential component of central monitoring, but their implementation is far from simple. They need to be defined, programmed, tested and validated. In addition, they typically make use of only part of the data collected in a clinical trial. The threshold value that triggers a KRI is typically an arbitrary value that may vary from trial to trial, from region to region, and over the course of a trial.

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. An alternate approach, Central Statistical Monitoring (CSM), can be considered "bottom up," because it uses the data itself — potentially all clinical and administrative data — to identify possible issues. CSM can thus detect unanticipated problems in unexpected places.

The CSM Method

The comprehensive nature of CSM lends statistical credibility to study results and minimizes the chance that a study might have to be repeated due to a systemic problem that is detected too late. Because CSM reduces reliance on human judgment, CSM-based monitoring is more consistent across studies.

In a clinical study, once a piece of data has been collected, there is no reason it should not be used to monitor study performance. While primary outcome variables are typically scrutinized for errors or omissions, secondary variables receive less attention and may, thus, be more indicative of problems at a site. Even patterns in 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 the samples on that day needs training.

Anomalies in structured datasets are easily detectable, especially by multivariate and longitudinal statistical analysis.[4-6] 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.[7] Administrative data can be similarly grouped. Data is also categorized by study arm — baseline and administrative variables should not differ between the randomized 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.

The use of statistical pattern analysis to uncover fraud in multicenter trials has been the subject of academic discussion for many years but has been largely overlooked in monitoring activities.[4,5,8] CSM-based systems perform numerous statistical tests at all levels on properties of the dataset, such as means, variances, incidence of outliers, event counts, distribution of categorical variables, missing values, variation over days of the week, and multivariate correlations.[7,9] From these tests, a high-dimensional matrix of p-values can be generated to identify outlying sites and specific data to monitor.[6]

In addition to the normal objectives of site monitoring, CSM-based systems supplement standard data management and biostatistics tools for oversight of the quality of the data collected. They also help identify the best sites for future trials. They can even identify issues in sponsor or CRO performance.

CSM vs. KRI

The term "Central Statistical Monitoring" emphasizes the use of statistical analysis to drive the monitoring process. KRI-based systems can also employ centralized statistical measurements, but they are limited to pre-defined KRIs. While KRI-based systems rely on human judgment to define the KRIs and set threshold values, CSM-based systems let the dataset speak for itself.[10-12]

KRI- and CSM-based methods of RBM are complementary. 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 analyze data that is not accessible (e.g., handwritten notes and interviews); complex statistical analysis may be opaque

Most anomalous data is due to unintentional causes, such as ambiguity in the protocol, lack of training, or simple errors. KRI-based systems will detect such issues, provided they trigger a KRI, which are necessarily limited to a few important variables. In contrast, CSM-based systems detect a much more comprehensive range of anomalies without pre-programming.

KRI-based systems can also detect data falsification and fabrication, provided they trigger a KRI. Because CSM-based systems do not require pre-programming and test many more variables, it is very difficult to fool a CSM-based system.

Conclusion

Risk-based monitoring is much more efficient than 100% source data verification, but site monitors need guidance on when to monitor a site, whether to monitor in-person or remotely, and what data to inspect. KRI-based systems and CSM-based RBM systems can provide this guidance. Both approaches have strengths and weaknesses, so a hybrid approach is probably advisable for most studies. Regardless of the model used for risk-based monitoring, the statistical techniques used in CSM are essential for overall data quality oversight.

References

1. Morrison BW, Cochran CJ, White JG, *et al*. Monitoring the quality of conduct of clinical trials: a survey of current practices. *Clin Trials* 2011; 8: 342-9.
2. Medicines and Healthcare products Regulatory Agency. FAQs for monitoring. February 2013. Available at http://forums.mhra.gov.uk/showthread.php?1675-MHRA-produced-FAQs-for-monitoring/page3 (accessed 26 August 2014).
3. TransCelerateBioPharma Inc. Position paper: risk-based monitoring methodology. May 2013. Available at http://www.transceleratebiopharmainc.com/wp-content/uploads/2013/09/Risk-Based-Monitoring-Methodology-Position-Paper.pdf (accessed 26 August 2014).
4. Buyse M, George S, Evans S, *et al*. The role of biostatistics in detection and treatment of fraud in clinical trials. Statist Med. 1999; 18: 3435-51.
5. Evans S. Statistical aspects of the detection of fraud. In: Lock S, Wells F, Farthing M (Eds). Fraud and Misconduct in Biomedical Research. London: BMJ Publishing Group, 2001 (third edition).
6. Venet D, Doffagne E, Burzykowski T, *et al*. A statistical approach to central monitoring of data quality in clinical trials. Clin Trials 2012; 9: 705-13.
7. Lindblad AS, Manukyan Z, Purohit-Sheth T, *et al*. Central site monitoring: results from a test of accuracy in identifying trials and sites failing Food and Drug Administration inspection. *Clin Trials* 2013; Dec 2.
8. Pogue JM, Devereaux PJ, ThorlundK, and Yusuf S. Central statistical monitoring: detecting fraud in clinical trials. *Clin Trials* 2013; 10: 225-35.
9. Kirkwood AA, Cox T and Hackshaw A. Application of methods for central statistical monitoring in clinical trials. *Clin Trials* 2013; 10: 783-806.
10. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry: Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf (accessed 26 August 2014).
11. European Medicines Agency. Reflection paper on risk-based quality management in clinical trials. EMA/INS/GCP/394194/2011. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500110059.pdf (accessed 26 August 2014).
12. Baigent C, Harrel F, Buyse M, *et al*. Ensuring trial validity by data quality assurance and diversification of monitoring methods. Clin Trials 2008; 5: 49-55.

Author

Marc Buyse, ScD, is the Founder of CluePoints and an Associate Professor of Biostatistics at Hasselt University, Diepenbeek, Belgium. Contact him at marc.buyse@iddi.com.

