Under Surveillance: How Risk-based Monitoring Improves the Success and Efficiency of Clinical Trials

PEER REVIEWED

The biopharmaceutical industry, reeling under the pressures of low R&D productivity and increased costs of clinical development, has been looking at ways to do more with less. Clinical trial (CT) monitoring, which contributes to over 30 % of trial costs, has been a major focus area in this endeavour. On-site monitoring of clinical trials has been identified as one of the most cost and resource-intensive components of the clinical trial industry's global spending (over US $42 billion in 2012[1]).

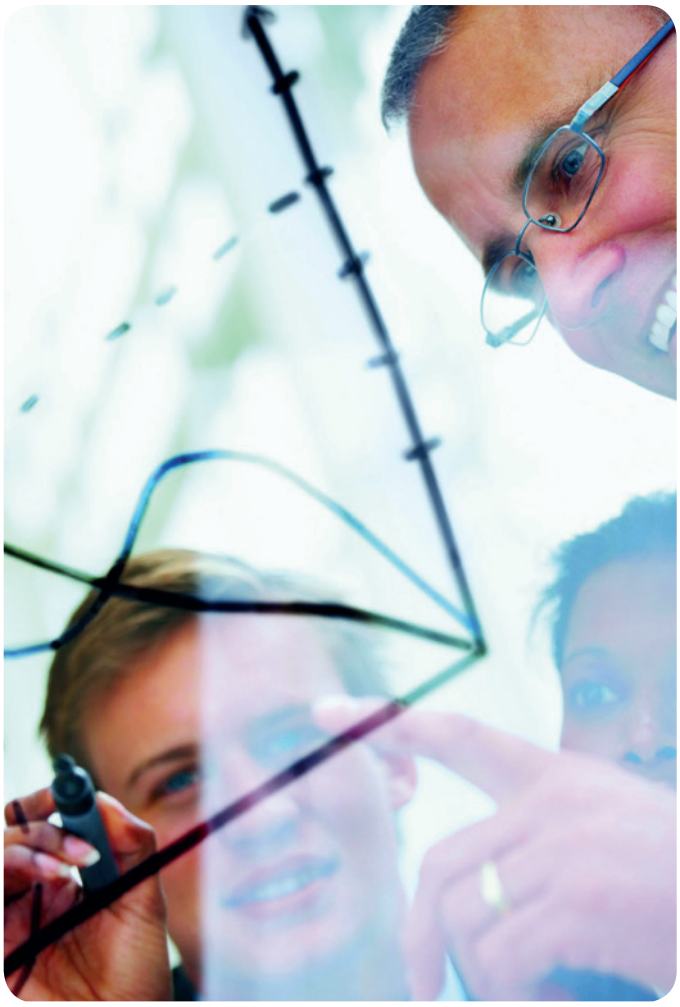
Smart approaches to monitoring, such as centralised, remote, risk-based and adaptive monitoring which are emerging, can reduce the need for on-site monitoring visits and source data verification (SDV) while achieving the objectives of monitoring more effectively. It is recognised that the traditional approach of on-site visits and 100 % SDV is not optimal, and cannot, on its own, effectively achieve the primary objectives of monitoring, which are to ensure the rights and safety of participants and the reliability of safety and efficacy results. Both the US FDA and European Medicines Agency are urging greater reliance on centralised monitoring practices to identify when on-site monitoring is truly required and how on-site monitoring can be optimised through metrics collected from centralised monitoring methods. The guidance released by the FDA in August 2013[2] recommends a quality risk management approach to CTs that encourages greater use of centralised monitoring practices which may be better suited for the risk-based monitoring strategies the sponsors are developing.

A Risk-based Approach to Monitoring

Key elements which are intrinsic to the reliability of safety and efficacy results from a clinical trial are: power of the study (which can be affected by recruitment numbers, treatment compliance, completeness of data and adequacy of follow-up information), inclusion criteria (to ensure that the study population is as intended and is homogenous), treatment allocation (randomisation and blinding) and outcomes (accurate measurement and capture of outcomes data and use of appropriate statistical methods for analysis and inference). Certain indicators of these elements are the factors for which risk assessment is performed in order to eventually determine the extent and frequency of on-site monitoring which is apt for the study. Some of these factors are: complexity of design (including study phase and types of endpoints), geographical spread, investigator experience, whether electronic data capture (EDC) is used and the safety profile of the product.

Approaches to risk assessment may be qualitative/subjective or quantitative/objective. For example, risk ratings can be qualitatively assigned based on study design, which is a major determinant of protocol complexity. Risk ratings can be assigned *a priori* depending on whether only non-invasive procedures are used (lowest risk – e.g., non-interventional/observational), only approved treatments are used (mild risk – e.g., Phase IV), whether it is a Phase III trial with a new treatment and/or a new indication (moderate risk) or whether it is a Phase I or Phase II trial of a new treatment (high risk).

An optimised monitoring strategy can be determined based on these risk ratings and key risk indicators (KRIs) corresponding to other factors such as patient safety (rates of adverse events and serious adverse events), treatment compliance (percentage of patients with delayed or reduced dose or with treatment discontinuation), data management (delays in completing and sending case report forms, query rates, query resolution times) and other aspects of study conduct (actual vs target recruitment rate, percentage of patients with protocol violations, percentage of dropouts).



A report of a pilot project conducted by Pfizer and the US FDA to test a model for prospectively designing quality into CTs and managing quality during study conduct illustrates the use of statistical methods in quantitative risk assessment[3]. This project, based on 73 ongoing studies, applied a quantitative

approach to complement integrated quality management plan (IQMP) efforts using statistical models to identify risk factors that require more scrutiny. Factors related to eight different risk categories were considered to identify perceived risks. The risk categories were compound characteristics, subjects, protocol, locations, site operations, outsourcing, monitoring and drug supplies. A statistical test (Wilcoxon rank sum test) was used to identify association between risk factors and the occurrence of quality issues. In univariate analysis, the following risk factors had at least a marginal association ($p < 0.1$) with the number of quality issues: packaging/labelling, dosing complexity, biologic compound, size of planned procedures, subjectivity in measurement, use of placebo and number of exclusion criteria.

Monitoring plans formulated on the basis of such risk-based assessments may sometimes include extensive on-site monitoring, but mostly will include reduced (risk-adapted, or on a random sample of centres/patients/outcomes) or targeted (based on KRIs and statistical monitoring) monitoring. The quality of study conduct is monitored through (a) training, (b) data entry checks and discrepancy management, (c) central and on-site monitoring of data and (d) planned checks by data monitoring committees (DMCs). Central statistical surveillance (CSS) is a critical element of central monitoring.

How Central Statistical Surveillance Adds Value

CSS is a centralised monitoring technique that uses statistical tools to identify errors, outliers and abnormal trends/patterns in clinical trial data, and thus provides effective triggers and leads for targeted monitoring visits.

Sources of errors are study design, study procedures, case report form (CRF) design, data recording, data analysis and inference. Errors can be random or systematic. Random errors may impact the statistical power of the study but may not result in bias, while systematic errors will most certainly result in biased conclusions. Errors could be unintentional (e.g. unknown issue with calibration of an instrument), could be due to lack of attention to detail (data not transcribed correctly from the source to the CRF) or due to a lack of understanding (unclear about how dose titration details are to be captured on the CRF). In rare instances, there could be deliberate errors committed with the intention to fabricate or falsify data. Results of a survey conducted a few years ago suggested that erroneous analysis, reporting and interpretation due to lack of knowledge and understanding were perceived to be far more common than intention of fabrication or falsification[4].

The main principles underlying the use of statistical methods to detect errors, outliers or trends are:

- Clinical trial data generated by application of a standard protocol and the same CRF at all participating centres is highly structured in the way it is collected, grouped and analysed.
- The multivariate structure and/or time dependence of the variables is sensitive to deviations and easily detected by statistical tests.

CSS is able to detect data issues that go undetected in SDV and on-site checks, e.g., identical values for vital signs over several visits. It considers every piece of information entered in the CRF as potentially indicative of quality rather than being restricted by pre-defined KRIs. Statistical checks are performed to check randomness (first digit preference, rounding), plausibility (correlation structure, outliers, dates in range) and comparability (between treatment arms, between centres or any other covariates of interest).

Basic statistical procedures and tests such as the Chi-square test, t-test and F-test are used to compare the distribution of all variables of interest across centres for the purpose of identifying any 'outlying' centres or observations. Study design and CRF design issues could also be detected from such analysis. For example, low variability in data across visits (indicated through the F-test) may lead to suspicion that the same observation is being entered without actual measurements being taken at each visit. This may suggest that the CRF has too many fields and its size may need to be reduced. Plausibility checks (for correlations, outliers) may require appropriate plots and graphs, followed by statistical inferential procedures. Model-based approaches are required to check comparability across centres. Tests on means, within patient variances etc., are used to generate a high-dimensional matrix of p-values with statistical methods used to identify outliers.

A recent article provides results from actual trials to illustrate typical findings that can be expected from a CSS approach which detects abnormal patterns that were not (or could not have been) detected by on-site monitoring[5]. Data fabrication or falsification done with an intention to hide missing data or to make the results look more favourable for a particular treatment, may be detectable through centre or treatment-by-centre comparisons from appropriate statistical models that are fitted to the data. A recent publication illustrates the development and validation of risk scores to identify fabricated data within a multicentre trial, to be used in CSS[6]. The analysis was based on a database from a multicentre cardiovascular trial in which data from 9 to 109 centres was documented to be fabricated. Exploratory factor analysis was used to select from 52 possible predictors. Final models were selected from a total of 18 independent predictors and the models were converted to risk scores for each centre. Five different risk scores were identified and each had the ability to discriminate well between centres with and without fabricated data. The risk scores were validated for their false-positive rates.

CSS relies on 'sufficient' data being available to be able to detect abnormal trends. Hence it may not be effective in trials that have several centres with small amounts of data, or at the beginning of a trial before sufficient data is accumulated.

Conclusion

Results of a survey published in 2011, based on the responses from 65 organisations performing clinical trials, indicated that 83 % use centrally available data to evaluate site performance and 12 % always or frequently used centralised monitoring to replace on-site monitoring[7]. In this survey, 87 % of respondents said that they always perform on-site visits. However, the reliance on central and remote monitoring has increased significantly of late and organisations have embraced a risk-based approach to on-site monitoring.

In summary, an efficient and effective monitoring strategy is a combination of (1) targeted site visits, primarily for training, mentoring and support to site staff, (2) remote assessment through incident alerts, tracking system and statistical analysis and (3) trial oversight through steering committees and DMCs. CSS is a powerful tool which can identify unexpected or strange data patterns, making on-site monitoring much more targeted and effective. It is critical for an effective risk-based monitoring strategy. Its growing importance is indicative of the crucial role of statistics and programming in effective clinical trial monitoring and hence the need for the sponsor to ensure availability of statistical expertise while planning resources for monitoring. If the sponsor is managing the trial in-house, adequate statistics and programming resources would have to be planned for each study. If the trial is outsourced to a contract research organisation (CRO), the sponsor will have to ascertain that the CRO has the capability to perform CSS or they may have to use another vendor for this activity.

References

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