With global R&D spend being well over $100 billion, approximately 40% goes into clinical research. In fact, the clinical trial industry’s global spending exceeded US $42 billion in 2012. On-site monitoring of clinical trials has been identified as one of the most cost and resource-intensive components - contributing to over 30% of trial costs.

Moreover, it is estimated that only about 50% of the monitor’s time is actually spent on monitoring activities, while the rest is spent on travel, logistics and reporting. In view of the low R&D productivity and major cost pressures on the pharmaceutical industry over the past decade, it is hardly surprising that there has been an increased focus on reducing the cost of Clinical Trial (CT) monitoring by making the process more efficient.
Centralized, remote, risk-based and adaptive monitoring are effective strategies which reduce the need for on-site monitoring visits and source data verification (SDV), while achieving the objectives of monitoring through more effective means. This concept was explicitly mentioned in ICH E6, paragraph 5.18.3 which mentions central monitoring and how and when it could be used. US FDA’s 21 CFR Part 312 (Sponsor’s Responsibilities) also provides flexibility on monitoring strategy to the sponsors. However the focus from the regulators and the industry on these monitoring approaches is recent.

Indeed both the US Food and Drug Administration (FDA) and the European Medicines Agency are urging greater reliance on centralized monitoring practices to identify when on-site monitoring is truly required, and how it can be optimized using metrics collected by centralized monitoring methods.

The FDA’s Guidance for Industry Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, released in August 2013, recommends a quality risk management approach to clinical trials. It encourages greater use of centralized monitoring practices and other alternate monitoring approaches, which may be suited as sponsors develop risk-based monitoring strategies.

Objectives of Monitoring

The overarching objective of monitoring is to improve the availability of reliable data from clinical trials which are used to assess and endorse safety and efficacy of new treatments. Monitoring should enhance the ‘quality’ for study participants and also for future patients who will receive the medicinal products approved on the basis of regulatory submission of data from clinical studies.

The purpose of monitoring is to ensure the rights and safety of participants and the reliability of safety and efficacy results. Informed consent, data privacy and confidentiality are participants’ rights. Safety is protected by monitoring the hazard of the treatments or interventions and also any harm that may be related to assessment or follow-up.

A few key elements intrinsic to reliability of safety and efficacy results 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 (randomization and blinding) and outcomes (accurate measurement and capture of outcomes data and use of appropriate statistical methods for analysis and inference).

The default, resource-intensive monitoring, which traditionally consists of on-site visits and 100% SDV, is no longer considered an optimal method because it cannot achieve the primary objectives of monitoring without other complementary approaches working in tandem. With this in mind, most companies now adopt a risk-based approach to determine the optimal monitoring strategy for each study.
A major determinant of protocol complexity is study design. Studies can be assigned risk ratings *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 4), whether it is a phase 3 trial with a new treatment and/or a new indication (moderate risk) or whether it is a phase 1 or phase 2 trial of a new treatment (high risk).

An optimized monitoring strategy can be determined for every new study on the basis of these risk ratings. Modification and customization of the strategy may be required for individual investigator sites based on key risk indicators (KRIs) related to aspects of study conduct, patient safety, treatment compliance, and data management. It is important to identify the KRIs upfront so that the metrics required to evaluate and monitor them can be generated and reported on a regular basis. KRIs are related to aspects of study conduct (actual vs target recruitment rate, percentage of patients with protocol violations, percentage of dropouts), safety (rates of adverse events and serious adverse events), treatment compliance (percentage of patients with delayed or reduced dose or with treatment discontinuation) and data management (delays in completing and sending case report forms, query rates, query resolution times).

A hybrid monitoring approach is determined by factoring in the risk ratings and KRIs. The monitoring plans may sometimes include extensive on-site monitoring, but mostly include reduced (risk-adapted, or on a random sample of centers/patients/outcomes) or targeted monitoring (based on KRIs and statistical monitoring). In this advanced approach the quality of study conduct is monitored through:

- Training, mentoring and oversight of site staff
- Data entry checks and discrepancy management
- Central and onsite monitoring of data
- Planned checks by data monitoring committees (DMCs)

Central statistical surveillance (CSS) is a critical element of central monitoring.
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 almost 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 falsification⁴.

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 KRs. Statistical checks are preformed to check randomness (first digit preference, rounding), plausibility (correlation structure, outliers, dates in range) and comparability (between treatment arms, between centers or any other covariates of interest).

Basic statistical procedures and tests such as Chi-square test, t-test and F-test are used to compare the distribution of all variables of interest across centers, for the purpose of identifying any ‘outlying’ centers 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 and statistical methods are used to identify outliers.

How Central Statistical Surveillance Adds Value

CSS is a centralized 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.
A Case Study

A global mid-sized pharmaceutical company initiated a CSS program to monitor study quality and Sciformix was selected as its statistics and programming partner.

One of the multi-center oncology studies was for the medullary thyroid cancer, stratified by histology. The objectives of the surveillance program were to review and monitor key aspects of the data on a monthly basis, including study population, study conduct, adherence to protocol, and information that may impact the quality of the study results. This was done in order to take corrective actions to improve data quality, in particular, to determine the need for risk-based monitoring visits to certain investigator sites.

Sites completed their CRFs and were required to make data available within five days; and data clean-up and transfer from clinical data management (CDM) was expected in seven days. The data monitored included protocol violations, subject disposition, demographic and baseline characteristics, safety data such as Adverse Events and abnormal laboratory values, efficacy data on specified tumour response measurements, and missing or incomplete data. The Sciformix team generated tables, listings, graphs (TLGs) and patient profiles on a monthly basis.

The client’s program statistician and program clinical lead, along with the Sciformix project statistician were the primary reviewers to detect potential site-specific issues in study conduct and quality and to detect any other trends in the data. Immediate steps were taken as required with respect to additional monitoring and SDV at certain sites, query resolution and any other corrective actions required in order to ensure that patient safety and efficacy is not compromised.

CSS involved monitoring of the following key safety and efficacy data for this oncology study.

- Protocol violations, involving use of prohibited medicines, assignment to wrong stratum by histology, skipped or incomplete tumor assessments etc.
- Subject disposition, in particular data for discontinued patients
- Demographic and baseline characteristics, such as reproductive status, method of contraception, ECOG score, baseline diagnosis by histology and prior therapies

...How Central Statistical Surveillance Adds Value

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 center or treatment-by-center comparisons from appropriate statistical models that are fitted to the data.

However, 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 are accumulated.
...A Case Study

- Safety data, primarily about adverse events, abnormal laboratory values, actual dose taken in each cycle and concomitant medications.
- Efficacy data on tumor response, primarily the sum of the longest diameter for each target lesion and the percent change from the smallest previous diameter, investigator’s tumor time point response assessment and status of the non-target lesions.
- Missing and incomplete data, by CTC grade when applicable.

Data monitoring typically requires patient profiles, listings, or simple statistical procedures such as scatter diagrams, box plots and a descriptive statistical summary of the data to detect outliers or unexpected, underlying data patterns. To an experienced pair of eyes, potential outliers or unexpected data patterns can quickly jump out from scatter diagrams and box plots. However, in this example greater statistical sophistication was required to explore missing data and to differentiate between ‘monotone’ missingness and ‘intermittent’ missingness.

Through two types of analyses – longitudinal analysis (without any imputation of missing data) and the last observation carried forward (LOCF) analysis, confidence intervals for the primary efficacy variable were calculated, uncovering a large difference in the two confidence intervals. These findings resulted in further investigation of the missing data and substantial corrections in study conduct were implemented to reduce the incidence of missing data.

Statistical monitoring of the rest of the data led to detection of a pattern in the status of investigator’s tumor time point response assessment at one site which led to greater data scrutiny and monitoring. At another site, study staff misunderstanding regarding the recording of the actual dose in each cycle was uncovered, resulting in the provision of additional training. A few other issues were also identified and addressed.

CSS was very effective for this study, with the client being able to detect and fix issues in time and use monitoring resources in an optimal manner.
Conclusion

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.

In summary, 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 will have to be planned for each study. If the trial is outsourced to a Contract Research Organization (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.

Sciformix, with its expert team of statisticians and programmers, is often called to perform CSS, either as part of end-to-end Biometrics support for a study or as a standalone activity even if the client is using a different vendor for statistics and programming support for the study.

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