HOW DO SPONSORS ENSURE QUALITY IN GLOBAL CLINICAL TRIALS?

Understanding potential pitfalls and how to avoid them using technology-based solutions

Clinical trials today are increasingly complex and when conducted on a global scale, the need to ensure high levels of quality becomes critical. As early as 2010, the Office of Inspector General, U.S. Department of Health and Human Services, reported that 80% of approved applications for drugs and biologics in fiscal year 2008 contained data from foreign clinical trials, with over half of study sites and subjects being located outside of the United States.[1] Factors contributing to this trend include, but are not limited to:

- Need to recruit patients faster in order to increase first-to-market opportunity/advantage;
- Sponsors' desire to deliver drugs/devices to a specific population of patients;
- Regulatory mandates stipulating that a minimum number of patients must be recruited from a particular country/region;
- Economic incentives related to the cost of conducting a clinical trial;
- Improved ability to identify and recruit a group of patients who do not have access to a particular therapy or class of drug.

Regardless of the reasons, global clinical trials seem to be the trend and gaining in popularity, but running a global trial is not a straightforward process. This white paper explores some of the challenges associated with global clinical trials and considerations for ensuring that the collected data comply with the trial's overall objectives.

The Challenge of Global Enrollment

Clinical research trials offer an opportunity for patients who may not ordinarily have access to contemporary standard of care therapies due to cost and/or reimbursement issues, to receive novel therapies; as a result, these patients are often highly motivated. However, this practice has recently come under scrutiny.

Take, for instance, the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) study of spironolactone vs. placebo in patients with heart failure with preserved ejection fraction. The trial included over 3,400 subjects in the United States, Russia, Georgia, Canada, Brazil and Argentina, reporting no significant reduction in the composite of death from cardiovascular causes, aborted cardiac arrest or hospitalization for management of heart failure.[2]

A post-hoc analysis of TOPCAT showed that important regional differences existed in terms of baseline characteristics of study participants as well as occurrence of endpoints between Russia/Georgia and the rest of the countries,[3] noting that a larger number of subjects from Russia/Georgia were enrolled in the study on the basis of having a heart failure hospitalization and not necessarily on the basis of an elevated brain natriuretic peptide (BNP) level, a biomarker with greater sensitivity and specificity to confirm a diagnosis of heart failure. Moreover, these subjects in Russia/Georgia were less likely to have an outcome event over the duration of the study.

A more recent sub-analysis of serum samples for the spironolactone metabolite, canrenone, showed that 30% of the Russian subjects assigned to spironolactone who reported to be taking the drug at 12 months had no detectable levels of canrenone. This is compared to 3% of the subjects tested from the United States and Canada,[4] making the interpretation of study results difficult given this discrepancy.

In 2017, the Trial of Ularitide Efficacy and Safety in Acute Heart Failure (TRUE-AHF) study of ularitide vs. placebo in patients with acute heart failure, conducted in 23 countries, including the Americas and Western/Eastern Europe, showed that while there was some physiologic improvement, this did not translate into significant mortality benefit.[5] Further analysis of the data contends that 17% of subjects enrolled in the study were ineligible and that 63% of sites in Czech Republic, Estonia, Poland and Serbia enrolled three or more ineligible subjects.[6]

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When clinical trials must be conducted globally in order to enroll the right patient population, the necessary number of subjects, and meet timelines, how can the trial sponsor ensure that collected data comply with the trial's objectives?

The Importance of Global Trial Management

Execution of global clinical trials requires interaction with regulatory authorities and investigators in multiple countries. A sponsor of clinical trials typically relies upon a global CRO or a host of local CROs to facilitate such interactions. While local CROs might be attuned to their respective regional environments, only a global CRO can ensure consistent execution of the trial across all regions. Global CROs like Covance have invested substantial effort and resources in developing technology, networks of vetted investigators, and organizational and operational procedures to ensure consistent patient management and high quality data collection across the participating sites.

Successful management of global clinical trials requires considerable planning and oversight, which can be greatly enhanced through technology. Covance leverages the Xcellerate® Informatics Suite of applications to ensure quality and efficiency throughout the study design, site monitoring and data management stages. Xcellerate Trial Design utilizes a vast amount of proprietary data on historical site performance and patient availability along with advanced combinatorial optimization techniques to identify sites that can optimize speed, enrollment and cost without compromising quality. Xcellerate Monitoring delivers tailored visual analytics to facilitate central monitoring of study risks, patient safety and data quality. Lastly, Xcellerate Insights provides near-real-time access to key performance and quality indicators to ensure effective global management and oversight.

Creating Success Through Site Selection

Site selection starts by choosing an optimal set of countries based on local regulatory requirements, healthcare practices, standards of care and the availability of quality sites and suitable patients, among other factors. The final site list is determined based on the results of feasibility surveys, site risk assessment and contract negotiations.

To facilitate country and site selection, Covance uses a broad range of inputs. In addition to leveraging our medical and scientific expertise, the regulatory and operational experience of country teams and our established relationships with investigators and research hubs, we also utilize various proprietary and commercial data sources coupled with sophisticated optimization algorithms embodied by the Xcellerate Trial Design tool.

As a market leader in central laboratory services, Covance has assembled the most comprehensive investigator database in the pharmaceutical industry, spanning more than 12,000 protocols, 600 clinical indications, 180,000 unique investigators, and 15 million patient visits over the past 10 years. Our Xcellerate Trial Design platform leverages these vast amounts of historical data to enable clinical trial planners to intelligently identify and prioritize high performing sites when planning a new trial. In brief, our methodology uses the metadata associated with the laboratory kits that we receive from the different clinical sites (such as trial and anonymized patient identifiers, investigator names and addresses, sample collection and shipment dates, etc.) to reconstruct the complete schedule of subject visits, and use these visits to develop reliable metrics and insights about the operational performance of the respective sites. Using this historical performance data as part of a multi-dimensional input matrix, our Xcellerate Country and Site Optimizer uses advanced optimization algorithms and data visualization displays to rapidly sift through the myriad of possible combinations to identify which countries and specific sites to use for a given protocol, and allow study teams to compare different scenarios and evaluate the trade-offs between trial length, logistical complexity and cost.

Another key criterion for site selection is patient availability. In the past, we relied upon estimates obtained from the sites. Now, as part of LabCorp, the world's largest healthcare diagnostics company, we are able to utilize de-identified diagnostic data for more than 100 million lives to understand available patient populations down to a specific geographic location. Combined with the investigator knowledgebase derived from our central labs, these data assets allow us to address questions such as whether it is feasible to recruit patients to the current study design, how to optimize site networks based on historical performance data and available patient populations, how to be more precise and confident about country allocation, how to optimize the inclusion and exclusion criteria, and how to predict enrollment based on epidemiology and prevalence at a specific location. Because of the dominance of Covance and LabCorp in the clinical laboratory market, these data assets are unique and unrivaled in scale, depth and breadth.

Educating and Monitoring the Sites

Consistent investigator training is an important consideration for all global studies. Covance provides initial training to the study team at the time of the site initiation visits as well as during investigator meetings to ensure compliance throughout the trial. Following this initial training, Covance monitors data collection and key performance/risk indicators such as protocol deviation trends, adverse and serious adverse event rates, enrollment rates, timeliness of data entry, query rates, and many others. Study monitoring allows us to identify performance deviations at the local, regional and study level that can be corrected through targeted retraining based upon specific, observed study challenges.

The Xcellerate Medical Review tool is a powerful means to help the study team identify potential issues regarding study conduct at the sites. Take, for instance, the following example: In a recent Alzheimer's disease trial, a cluster of transient ischemic attacks occurring in a narrow time window during the screening period were identified within one month after entry into the electronic data capture system. Having been tracked to a single site, these were found to be potentially attributable to a study procedure. This information allowed timely intervention at the site level by the Sponsor.

In this same trial, adverse events are being monitored rapidly and efficiently across all their major attributes (frequency, severity, seriousness, time of onset, action taken, etc.), not just in aggregate, but also at the site level, using standardized but highly customizable visualizations for easy detection of outliers.

Additionally, centralized monitoring of key eligibility criteria has allowed not only the early identification of potential violations at enrollment, but also tracking of the reasons for screen failures. Tracking the reasons for both screen failures and discontinuations permits continuous assessment of important sources of bias at the site and country levels.

Tracking Risk and Trial Monitoring

A strategy for proactively identifying and mitigating risks helps to avoid unnecessary study delays and ensures ongoing patient safety. The recently released ICH E6 R2 guidance emphasizes the importance of the multi-prong approach for study quality assurance combined with an upfront definition of the tolerance limits for quality deviations and mitigating actions when the thresholds are exceeded. The guidelines call out development of a systematic, prioritized, risk-based approach to study monitoring combining both on-site and centralized monitoring activities. Specifically, the guidelines include routine review of submitted data by medical experts; use of statistical techniques to identify missing, inconsistent or outlying data that may be indicative of systematic or significant errors in data collection and reporting; analysis of site characteristics and performance metrics; and selection of sites and/or processes for targeted on-site monitoring.

Quality by design and risk-based monitoring (RBM) of a clinical trial starts with a systematic study risk assessment facilitated by the Xcellerate Risk Assessment and Categorization Tool (RACT). Identified study risks that require monitoring throughout the trial are encoded as key risk indicators and are periodically reviewed by the operational experts using the Xcellerate Risk Review dashboard. This periodic review allows us to divert more monitoring resources to sites with higher risks and prevent emerging issues from becoming systemic. Issues with patient eligibility, like the one that affected the outcome of the TRUE-AHF study, and patient safety are monitored through a periodic review of aggregated patient data facilitated by Xcellerate Medical Review. The Xcellerate Data Review application is used to track data entry based on the visit schedule, and monitor critical data capture and report data readiness for database lock.

Lastly, Xcellerate Statistical Review applies statistical techniques to detect non-random data anomalies across sites that may indicate data collection bias, sloppiness or downright fraud. For example, the issue with non-detectable levels of canrenone in subjects from Russian and Georgian sites reported in the TOPCAT study could have been easily detected through statistical review while the trial was still ongoing.

Keys to Avoiding Pitfalls in Global Clinical Trials

While Covance was not involved in the recent studies that identified potential pitfalls in global clinical trials, we believe we are able to detect the issues early on or avoid them altogether. The main problems reported in the TOPCAT study were recruiting unsuitable patients in Russia and Georgia and the undetectable quantities of the study drug's metabolite. Recruitment of unsuitable patients could have been prevented through improved site selection methodologies based on past site performance and/or adequate medical review of the enrolled subjects. Sites without prior experience in clinical trials or with known performance issues could have been avoided or

assigned higher monitoring scrutiny based on the pre-study site-risk assessment. Working with the Covance central labs and bioanalytical facilities, a comprehensive global testing strategy could have been developed encompassing safety testing, biomarkers and drug metabolites.

In the TRUE-AHF study, the reported reason for ineligibility was violation of stability or safety criterion. It is likely that these deviations could have been detected through the use of Xcellerate Medical Review; an early analysis of the sites recruiting ineligible patients would have allowed for site retraining and correction of the problem before it had adversely impacted the analysis of the trial's data.

While global clinical research trials afford numerous opportunities, challenges may also be introduced. A proactive approach to identify experienced investigators with access to the appropriate patient population, providing education to site staff over the course of a clinical trial, and monitoring data quality and site performance metrics ensures study integrity.

References

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