Boosting Trial Success through Blinded Data Analytics: What Can We Learn from CNS?

Research scientists know that data alone do not lie – but data can mislead. That's especially true in clinical trials that rely on subjective endpoints to assess drug efficacy.

Psychiatry studies, for example, which often centre around the clinician's assessment of disease progression or severity, have modest success rates. Just 24% of Phase II and 56% of Phase III psychiatric studies1 demonstrate a statistically significant drug-placebo separation. But is it true that so many medications, having moved so far through the development pathway, do not work, or is something else at play?

In truth, the reasons for these modest success rates are multifactorial, but often excessive placebo response rates and lack of precision in measurement of symptom severity are root causes of trial failure. Electronic clinical outcome assessment (eCOA)-based technology, combined with sophisticated data analytics, has the potential to address many of them.

Quality Data

Signant's clinical data experts have demonstrated in central nervous system (CNS) clinical trials, including schizophrenia, Alzheimer's Disease and major depressive disorder, that data quality markers are predictive of measurement error, placebo response and diminished drug-placebo separation. This is likely to be equally true in other therapeutic areas that are reliant on subjective or "soft" endpoints.

Illustrative of this point are data collected on 4245 subjects participating in six atopic dermatitis (AD) trials across 286 investigative sites. The data were analysed for anomalies in the body surface area (BSA) assessments obtained during the administration of two rating scales, the Scoring Atopic Dermatitis (SCORAD) and the Eczema Area and Severity Index (EASI).

Using blinded data analytics, sites with aberrant measurement technique were identified. These sites recorded notably discordant body surface areas (BSA) on the same patients, utilising the SCORAD and EASI, despite each measure asking for the same assessment. The analysis was also able to identify erratic results, such as extreme fluctuations in symptoms and assessment scores from visit to visit, recorded by individual clinicians, or raters.

These common data quality errors have the potential to significantly undermine the success of a clinical trial.

Signant has worked with numerous CNS sponsors to help embrace data analytics programmes, informed by clinical insight and coupled with remediation, to significantly improve endpoint reliability. The same methodologies could now lead to similar benefits for any non-CNS fields which also struggle with low success rates.

Common Problems with Endpoint Data Quality

For a trial to yield meaningful results, the most relevant outcomes need to be measured in the most consistent manner. To that end, ensuring endpoint data quality rests upon establishing and maintaining precision of symptom measurement and early detection and remediation of poor-quality endpoint data.

Traditional outcome scoring lends itself to error, as the AD example of raters recording two values for the same measurement when using different scales illustrates. Paper-based assessments and manual calculations can result in collection of incomplete or erroneous data: mathematical mistakes or the omission of vital information, for example.

When raters are insufficiently trained and monitored on administering an instrument, trials can collect poor quality data. This can be a challenge. In today's world of global, multi-site investigations, each study could have hundreds of raters speaking dozens of languages in multiple countries, yet data integrity requires each of them to carry out the assessment and record the results in the same way.

Endpoint Quality Solutions

As has been demonstrated in CNS trials, integrated clinical trial software combined with clinical expertise and sophisticated data analytics can improve endpoint reliability.

Intelligent electronic clinical outcome assessment (eCOA) systems replace paper data collection and calculations. Quality platforms can include mandatory fields and provide memory-nudging hints and tips on performing the scale at hand, for example, and can monitor data input to flag quality issues in real time.

Similar systems will also be accessible to trial participants, meaning they can collect rich data from sources such as patient-reported outcomes (PROs) and symptom diaries and subject them to the same level of scrutiny.

Sponsors and CROs also need to know that every rater understands and administers the clinical assessment in the same way every time.

Best practice, systematic rater training and certification ensures sponsors can be confident that they are collecting like-for-like data across multiple sites, in multiple languages and cultures.

As many trial organisers will appreciate, data quality issues often remain hidden until the end of a study, which is why no trial strategy should ignore the importance of data quality monitoring.

Clinically informed, blinded, evidence-based data analytics can detect and remediate a lack of precision in subject interviews, improper diagnosis and symptom measurement, protocol non-compliance, procedure violations, and fraud.

Blinded Data Analytics — Success and Potential

Monitoring data quality for aberrant or illogical patterns of symptom change has been performed unobtrusively in the background of CNS trials, where it has informed the remediation of aberrant raters and sites.

In the AD analysis, for example, blinded data analytics were able to identify erratic scoring. This alerts sponsors to training needs before any lasting damage is done to the trial. This success can be replicated across any therapy area where trial failure is a result of the collection of poor quality data, or poor data collection processes, rather than a lack of drug efficacy.

Much like CNS studies, trials in immune-mediated conditions such as rheumatoid arthritis and inflammatory bowel disease, for example, rely heavily on rater-dependent assessments and patient-reported outcomes. And as such, they lend themselves well to similar blinded data analytics.

Data collection issues are common in areas such as cardiorespiratory disease, where manual collection often results in the rounding up or down of assessed values.

And oncology, for so long dominated by the "hard" endpoint of tumour response, is starting to embrace "soft" endpoints and PROs as a therapy's impact on quality of life becomes ever more important. Ultimately, blinded data analytics can be employed in all these areas to improve endpoint quality. This avoids costly trial failure, and, crucially, ensures new treatments are available to the people who need them as quickly as possible.

REFERENCES

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