WHITE PAPER

Safety as a Science: Analytics for Trial Safety and Pharmacovigilance

revvity signals

An essential element of pharmaceutical development is establishing the safety of a novel treatment. Analytical approaches are available to detect safety risks or benefits of proposed treatments in a therapeutic area. Pharmaceutical leaders need to better identify and manage drug safety in their clinical strategy.

Clinical trials can expose both predicted and unexpected safety signals. Surveillance must therefore look beyond expected adverse events to detect possible safety signals. Ruling out or exposing safety events through accelerated analytics can spare the rigorous data management and statistical resources required for submission while ensuring due diligence in clinical oversight of trial participant safety. Interim and final submission reporting can then focus on those safety events that are shown to be significant to the submission.

Multiple data sources are available during trial conduct. Those data accessible early in trial conduct provide opportunities to adjust trial data collection practices and site training. Furthermore, the trial amendment or clinical program strategy for upcoming clinical trial designs can be modified in response to emerging questions. Access to and automated aggregation of clinical data are essential to enable this early understanding of emerging safety signals while implementing and executing a clinical development program.

In a recent webinar, "Safety as a Science: Analytics for Trial Safety and Pharmacovigilance," experts from Revvity Signals explored the emerging capabilities that automate and accelerate the understanding of drug safety and facilitate decision-making and drug development strategy. Speakers for the event included:

- Brent Meyers, Executive Director, Clinical Analytics
- Dr. Philip Ross, Strategic Clinical Analytics
- Dr. Tsun-Hsuan (Joy) Chen, Sr. Clinical Analytics Consultant

From CRF safety data review to operational accelerators to in-house safety data, a pharmacovigilance database can offer crucial insights into an organization's clinical programs. Revvity Signals, a global company serving multiple industries, has developed several key analytics solutions for the biopharmaceutical industry, including pharmacovigilance, medical review, risk-based monitoring, and other core platforms powered by Tibco Spotfire®.

Safety Science and Pharmacovigilance

Biopharmaceutical companies face a number of safety data review issues, including slow data access, decentralized data, inflexible toolsets, and siloed tracking and retention practices. Determining how best to aggregate safety data can be especially important, as it drives an organization's ability to flexibly query across various data streams to identify signals that may otherwise be obscured in siloed trial data.

Each type of data comes with challenges related to adequately interpreting it often, early safety data has not been thoroughly cleaned or queried, so balancing rapid analysis of this data with accuracy is sometimes difficult. The data "dirtiness" stems from patient data transcription, but also the need for medical coding, physician review, protocol amendments, standardization, etc.

This difficulty with raw data "dirtiness" is further multiplied by the variety of clinical trial data sources. The variety of sources stems from the specific protocol, therapeutic, or operational needs. Additionally, many organizations are still utilizing siloed tools such as Microsoft Excel to collect and store data that have limited analytical power and limited automation of data access and aggregation. Tools such as SAS, R, or MATLAB are often workhorses used to analyze this data for regulatory submission using scripted analysis. However, alternative visualization tools represent an advantage over these platforms for fast and flexible analysis, because they do not require the programming skillset required for scripted analysis and are more intuitive in their use. This gives members of a clinical team more direct access to query data, allowing for more varied data exploration and allowing the statistical team to focus on regulatory analyses.

Clinical Analytics Solutions for Better Data Querying

Safety signals buried within hundreds of lines of inert data are easy to miss. Transitioning from traditional data-handling practices to more comprehensive, agile approaches is critical to transforming this paradigm. Visualization tools like Tibco Spotfire® feature superior capabilities when it comes to data wrangling. Revvity Signals Clinical Data Review (CDR) module exemplifies this capability: CDR can connect to virtually any data at its source and transform disparate data structures to easily create clinically relevant visuals from SDTM and raw data sources alike. Users can modify or extend visualizations, filter subjects in unexpected ways, and explore variables like efficacy, underlying pathology, or other key measures in a study without biasing a trial's conduct.

CDR's flexibility can allow users to easily see relationships and drill down on individual subjects within a trial in order to try to discover potential causes for any medical issues that arise during the study. This can help inform the course of a subject's treatment and even the study itself; for example, in examining the study subjects for drug-induced liver injury, a user can look at the subject or subjects with elevated levels of

bilirubin or alanine transaminase and determine if their levels were elevated prior to the onset of treatment. Other variables, such as whether a subject is taking a placebo or drug, and their age, sex, and medical history can all be easily accessed and cross-examined in CDR, affording users a powerful tool for gleaning insights during a trial.

The Revvity Signals Line Listing Review (LLR) module has additional key features in its medical review capability, which can afford trial teams an integral tool for collaboration and data querying in order to conduct review by a medical monitor. A medical monitor utilizing LLR can evaluate the adverse events reported by both frequency and severity and narrow events down by affected body system or organ class. If a particular adverse event is identified, the monitor can then query the trial team through LLR to request additional context regarding a specific subject or subjects. The date of each query and the number of open queries are visible on the dashboard, affording users easy tracking for safety and adherence purposes. Using Spotfire's advanced analytics across all areas of clinical development can help users minimize discrepancies, improve efficiency and collaboration among cross functional groups, and collect, visualize, and mine study data to achieve better trial management and overcome fundamental challenges.

Ensuring Safety for a Drug's Entire Lifecycle

Before a medicine is authorized for use, evidence of its safety and efficacy is limited to the results of clinical trials. Because clinical trial participants are carefully selected and closely monitored, the data is representative of a comparatively small patient sample tracked for a limited duration. After approval, this paradigm rapidly shifts, and a drug may be prescribed to millions of patients over many years and in combination with other therapies or in the face of other factors. Patient compliance becomes much more variable, inclusion criteria much less stringent, and side effects and adverse events may not be reported during a drug's use.

It is essential that the safety of all medications is monitored throughout their use in healthcare practice through pharmacovigilance. In addition to clinical trial data, pharmacovigilance data ideally includes spontaneous reporting from healthcare professionals and consumers, mandatory reports from manufacturers, and reports from active monitoring systems, as well as any data collected from non-interventional and non-clinical studies. By capturing data from as large a population as possible, a database can achieve a more accurate reflection of real-world performance of a drug.

There are multiple public data sources used for pharmacovigilance, including VigiBase, the World Health Organization's global database of individual case safety reports (ICSRs); the FDA Adverse Event Reporting System (FAERS); and Eudravigilance, which accrues data on adverse reactions to authorized medicines or clinical trial drugs in the European Economic Area (EEA).

Parsing pharmacovigilance data for verifiable insights can be a complex undertaking. With more than 2 million adverse events reported in FAERS alone in 2021, the need to identify safety signals through statistical analysis is more important than ever for the sector. This signal detection can help scientists identify patterns in large data sets; in doing so, they may discover new safety associations or new aspects of known associations. There are currently four major data algorithms being used to perform this signal detection – Empirical Bayes Geometric Mean (EBGM), Information Component (IC), Proportional Reporting Ratio (PRR), and Reporting Odds Ratio (ROR). Each was designed to uncover the same information, and differences between measurements for these algorithms should be small provided that the sample size is large.

The Revvity Signals pharmacovigilance solution, built in Tibco Spotfire®, is designed to help organizations actively monitor for adverse event signals in these large data sets. Users can query based on a specific drug or adverse event to identify those adverse events that occur at higher (or lower) frequency than expected, indicating a possible safety risk related to treatment or underlying disease. The Revvity Signals solution implements Bayesian algorithms that sift through the large data sets to indicate potential adverse event signals, some known in literature and others potentially novel. While this identification does not prove causation, it can offer critical insights for organizations regarding possible risk factors and at-risk populations, as well as facilitate risk evaluation and mitigation strategy development.

Revvity Signals data discovery and analytics solutions, including Clinical Data Review, Line Listing Review and Pharmacovigilance, empower clinical team users to go directly access the data, intuitively visually interact with it, perform ad hoc analysis, and gain insights previously not possible with fewer time delays.

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