Risks to signal detection in clinical trials: The relationships between operational and clinical risk in an ongoing phase 3 trial in schizophrenia.

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The Methodological Question Being Addressed: What are the relationships between identified operational and clinical risks?

Introduction (Aims): In the course of data-monitoring in a clinical trial there are a number of risk sources that emerge that should be addressed to maintain the integrity of study data. Operational risks include such things as visits occurring out of expected study window, missing or incomplete concomitant medications data, or even incorrect dosage. Clinical risks are those identified through inconsistencies in scale data, such as identical scores across multiple visits, clinically improbable change, or unexpected individual item correlations within a scale. Operational risks are often more obvious and require immediate follow-up with the study team, while clinical risks often require interaction with the site rater to determine if there was an actual error or if there is an unusual patient presentation. Both types of risk can endanger the success of the trial with missing or incorrect information, or reduction in signal detection due to poor clinical assessments (e.g., Kobak et al, 2009; Knepper et al 2016). In this study we explored whether these types of risks are related and, if so, in what way.

Methods: Results from an ongoing multicenter, global, Phase III clinical trial in schizophrenia were analyzed and operational and clinical risks were compared. Both types of risk were coded according to their frequency and severity and a total risk score was assigned per site. These scores were then compared. SPSS version 25.0 was used to test normalcy of the data before correlations were calculated for instances in which both operational and clinical risk were present.

Results: There were 122 sites (representing 20 countries and 2,638 patients) participating at the time of analysis. Of these sites, 11 (9%) had no associated operational or clinical risks; 9 (7.4%) had operational risks only; 37 (30.3%) had clinical risks only; 65 (53.3%) had both operational and clinical risks present. A Spearman's rank correlation was conducted for this non-parametric sample and approached a moderate correlation at $\rho = 0.259$, $p=0.037$.

Conclusions: There appeared to be a significant correlation present that approached the moderate level. Just over half (53.3%) of the sample contained both types of risk (operational and clinical). While often considered independently, their correlation suggests that this cumulative score is important in understanding the full picture, i.e., a site may have appeared reasonable from an operational or clinical perspective alone, but when combined provide a clearer indication of true risk. While the sample size is limited at this time, more data would confirm or deny this hypothesis. Future research might include whether there is some predictive capacity in the assignment of these risk scores, e.g., does operational risk predict clinical.

Disclosures: All authors are paid employees of Cronos CCS, a provider of risk-based data monitoring and related services to pharmaceutical trials.

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