Risks to Signal Detection in Clinical Trials: The Relationships Between Operational and Clinical Risk in an Ongoing Phase III Trial in Schizophrenia

Cynthia McNamara, Christian Yavorsky, Karen Meares, Brian K. Saxby, Kristy Wolanski, Francisco Burger, Guillermo Di Clemente
Cronos Clinical Consulting Services, Inc.

Introduction

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 in this analysis were identified through inconsistencies in PANSS and CGI-S data, such as identical scores across multiple visits, clinically improbable change, or unexpected individual item correlations within a scale: essentially any factor that impedes our ability to assess patient change over time. 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. These risks are identified by predetermined automated checks (data-monitoring algorithms) and subsequent intervention with the investigator. 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.

Objectives

To determine if there is a relationship between identified operational and clinical risks.

Methods

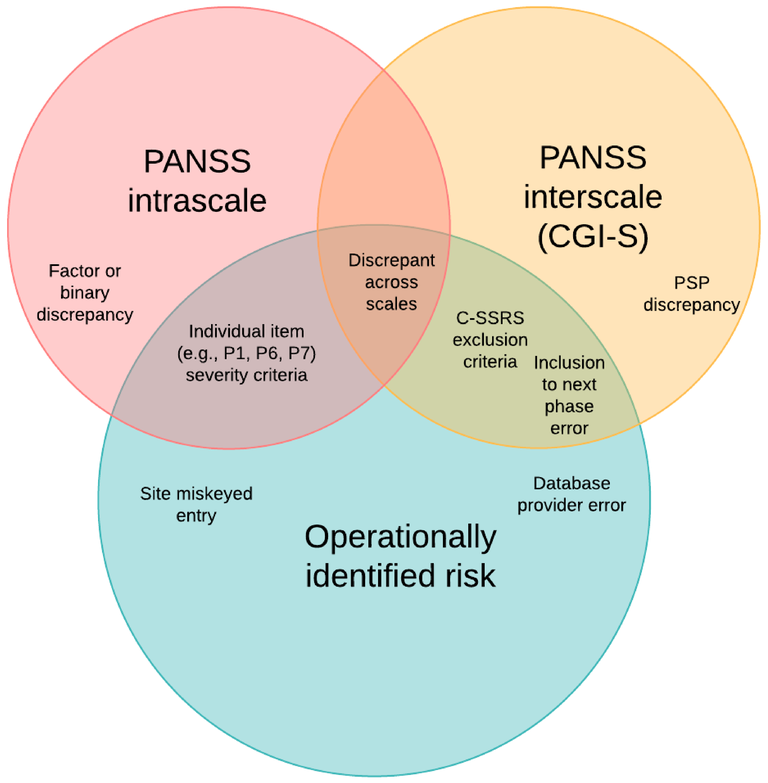
Results from an ongoing multicenter, global, Phase III clinical trial in schizophrenia were analyzed and operational and clinical risks were compared. Both types of risk were coded according to their frequency and severity and a total risk score was assigned per site. These scores were then compared. 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. The comparisons were between weighted severity in overall clinical and overall operational risk scores.

Disclosures: CM, CY, KM, BKS, FB, KW are fulltime employees, and GDC is the Founder & President of Cronos Clinical Consulting Services, Inc., provider of risk-based data monitoring and related services to pharmaceutical trials.

Corresponding Author: Cynthia McNamara, PhD; cynthia.mcnamara@cronosccs.com

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 ρ=0.259, p=0.037.



Conclusion

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.

Literature on operational risk in clinical trials (e.g., Tudur-Smith et al, 2014) focus on methods but also seek to establish thresholds whereby a certain percentage of data, if found to be incorrect, would trigger some action. Tudur-Smith and colleagues suggest this figure could be 5% of the data submitted by a site if it contained the types of operationally defined risks identified in this analysis such as out-of-window visits or missing data.

Ultimately this approach allows sponsors to make data-driven decisions about sites and more accurately target CRA visits. It is critical that during the course of the trial these problems are addressed to ensure that the data being gathered are not only present but accurate. Mitigation of in-study operational risks means more rapid database lock at the conclusion of the trial; mitigation of clinical risk may result in better signal detection from higher quality data.

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 risk.

References

Knepper D, Fenske C, Nadolny P, Bedding A, Gribkova E, Polzer J, Neumann J, Wilson B. Detecting data quality issues in clinical trials: current practices and recommendations. Therapeutic Innovation & Regulatory Science. 2016;50:15.

Kobak K, Brown B, Sharp I, Levy-Mack H, Wells K, Ockun F, Williams JB. Sources of unreliability in depression ratings. J Clin Psychopharmacol. 2009;29:82-85.

Tudur-Smith C, Williamson P, Jones A, Smyth A, Hewer SL, Gamble C. Risk-proportionate clinical trial monitoring: an example approach from a non-commercial trials unit. Trials. 2014;15:127.

Presented at the ISCTM 15th Annual Scientific Meeting 2019, Washington, DC