Procedures to Optimize Endpoint Data Quality in an Acute Schizophrenia Study

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SUBMISSION DETAILS

What is the Methodological Question Being Addressed? Is extensive rater calibration and data quality monitoring in an acute schizophrenia study associated with improved data quality compared to historical controls?

Introduction Schizophrenia clinical trials are particularly vulnerable to failure because they utilize relatively subjective endpoints and drug-placebo differences are often modest. We describe a phase 2b acute schizophrenia trial (KAR-004) in which an extensive set of procedures were employed to address accuracy and reliability of symptom measurement and modulation of placebo response. These procedures included 1) Site selection based on previous performance; 2) Pre-study calibration of interview and symptom severity measurement technique; 3) Placebo response mitigation training; 4) Operationalization and monitoring of acuity criteria; 5) Enhanced instructions and data quality checks embedded in eCOA; 6) Recording and independent expert review of PANSS interviews; 7) Blinded analytic review of endpoint data for concerning patterns; 8) Rapid remediation of rating and interview errors; and 9) Site enrollment continually tied to data quality.

Aberrant patterns of data variability may be associated with poor trial outcomes including diminished placebo-drug separation (Kott et al, 2017, a and b). The current analysis addresses the potential impact of the procedures described above on the prevalence of data variability quality concerns in a recently completed acute schizophrenia trial compared to acute schizophrenia historical controls.

Methods The percentages of visits affected with variability data quality concerns in a recently completed acute schizophrenia (n= 822 visits) study were compared to the percentages observed in historical controls (n=22,739 visits). The two cohorts were compared for the prevalence of 1) 30/30 items of the PANSS rated identically across visits; 2) 27-29/30 of the PANSS items rated identically across visits; 3) unexpectedly large changes in the PANSS total (outliers identified by Tukey’s method); and 4) erratic changes (10 point changes in opposite directions across three visits).

Results The percentage of affected visits was statistically significantly higher at the alpha level of .05 for historical controls vs. the current study for 100% identical ratings (2.3% vs. 0.5%), nearly identical ratings (14.5 % vs. 3.6%) and unexpectedly large changes (5.0% vs. 2.2%); but not for erratic ratings, which were infrequent in both cohorts (0.9% vs. 0.4%).

Conclusion In the current analyses, compared to historical controls, the percentage of visits affected by variability data quality concerns was statistically lower for three out of four quality

indicators in a recent acute schizophrenia study that utilized intense ongoing endpoint monitoring and restricted enrollment for poorly performing sites. Among the limitations in interpretation of the results are the use of historical controls rather than a prospective design and differences between the recently completed trial and historical controls in the countries and investigators contributing data. Future reports will address the impact of training and data quality indicators on placebo response and placebo-drug separation.

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Keywords

Keywords
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Guidelines I have read and understand the Poster Guidelines

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Alan Kott, David Daniel, Xingmei Wang and Christopher Murphy are employees of Signant Health.
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