Procedures to Optimize Endpoint Data Quality in an Acute Schizophrenia Study

Kott, A[1], Brannan, S[2], Wang, X[1], Murphy, C[1], Targum, S[1], Daniel, D[1]

[1] Signant Health, [2] Karuna Therapeutics

METHODOLOGICAL QUESTION:
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;
  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.

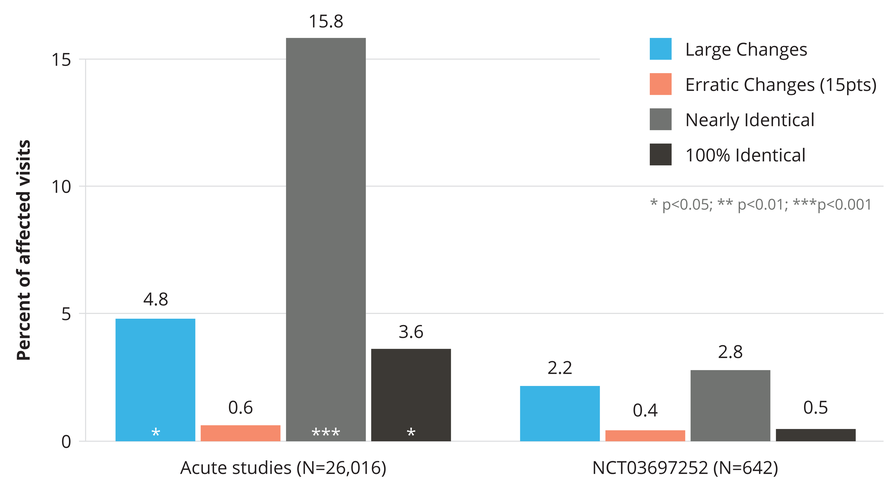
METHODS

- The percentages of visits affected with variability data quality concerns in a recently completed acute schizophrenia (n= 642 baseline and post-baseline visits) study were compared to the percentages observed in historical controls (n=26,016 visits).
- The two cohorts were compared for the prevalence of:
  1. 30/30 items of the post-baseline PANSS rated identically across visits;
  2. 27-29/30 of the post-baseline PANSS items rated identically across visits;
  3. unexpectedly large changes in the PANSS total (outliers identified by Tukey's method);
  4. erratic changes (15 point changes in opposite directions across three visits).

RESULTS

- As shown in Figure 1, 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 (3.6% vs. 0.5%), nearly identical ratings (15.8 % vs 2.8%) and unexpectedly large changes (4.8% vs. 2.2%); but not for erratic ratings, which were infrequent in both cohorts (0.6% vs. 0.4%).

Figure 1. Percent of Affected Visits



CONCLUSIONS

- 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.

DISCLOSURES

- A Kott, C Murphy, S Targum and D Daniel are full-time employees of Signant Health. Dr. Brannan is a full-time employee of Karuna Therapeutics.

REFERENCES

- Kott, Alan; Lee, Jeniffer; Forbes, Andy; Pfister, Stephanie; Ouyang, John; Wang, Xingmei, Daniel, David. (2017): Effect of High Within Subject Variance at Research Sites on Placebo Response and Drug Placebo Separation in Two Acute Schizophrenia Trials – A Post Hoc Analysis. Poster presentation. International Society for CNS Clinical Trials and Methodology (ISCTM). Paris, France, 9/1/2017.
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Presentation and associated analyses financially supported by Signant Health

Presented at the ISCTM 2020 Autumn Virtual Conference, September 21 - 25, 2020.

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