A Retrospective Analysis of the Effects of Protocol Design on Completion Rates in Outpatient Clinical Trials in Subjects with Schizophrenia or Schizoaffective Disorder

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INTRODUCTION

Subject attrition from randomized Schizophrenia trials is a significant problem and has been found in a meta-analysis to be as high as 76% (Robinowitz et al., 2005). The problem of drop-out is sometimes not addressed until the statistical analysis stage of a study which can decrease the validity of the results increasing the likelihood of a failed trial.

The authors **previously examined the effect of 9 trial design variables** on individual completion in **11 Phase I trials in subjects with stable Schizophrenia or Schizoaffective Disorder** at two clinical research sites in the period from 2009 to 2014 (Krefetz et al, 2015) The analysis showed that **shortening the length of the inpatient period, increasing the outpatient period, and shortening the longest period between outpatient visits had a positive impact on completion.** The data was reanalyzed in October, 2016 to evaluate the effect of **subject stipend** which **did not change the initial findings.**

The authors also studied an overlapping but similar dataset looking at the **impact of specific subject** characteristics **on early phase completion rates.** That analysis showed that the only significant predictor was that the **length of the current stability period at study entry** which had a positive impact on completion (Krefetz and Brown, 2016).

The authors now study the impact of eight protocol design variables on **study completion in outpatient clinical trials** in subjects with Schizophrenia or Schizoaffective Disorder.

Three additional variables (trial phase. study drug route, and primary aim of trial) were initially considered for this analysis but rejected due to initial statistical analysis indicating that due to insufficient variability, these variables biased the model.

OBJECTIVES

To study the impact of protocol design on individual completion rates in outpatient clinical trials in subjects with Schizophrenia and Schizoaffective Disorder.

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DESIGN

- The authors examined the effect **of 8 trial design** variables on subject completion in **17 outpatient Phase 2 through 4 clinical trials** of subjects with **stable Schizophrenia or Schizoaffective Disorder**.
- The 17 trials were conducted at either of **three clinical research sites** (Philadelphia and Southern New Jersey) operated by PRA Health Sciences or its legacy company, CRI Lifetree.
- All studies enrolled from **2010 to 2017.**
- These 17 trials enrolled **181 subjects** and had **overall completion rates ranging from 0 % to 100 %.**

Variables Studied include:

1. Length of trial from enrollment (12-68 weeks)
2. Longest period between visits (2-19 weeks)
3. Number of visits (9-20)
4. Period of stability required before screen (0-16 weeks)
5. Period since last trial required before screen (4-26 weeks)
6. Remain on (SOC) antipsychotic
7. Presence of placebo arm
8. Schizoaffective Disorder included

RESULTS

- Variables were analyzed via a **stepwise linear regression** analysis to assess the **predictive value of each independent variable** with regard to **study completion** (dependent variable).
- The following variables had **no predictive value** on study completion: **longest period between visits, number of visits, period since last trial required, presence of placebo, and inclusion of subjects with Schizoaffective Disorder.**

Predictive Values of Variables

	Odds Ratio	95% CI	p-value	Interpretation
Trial Length (weeks)	0.972	(0.952, 0.993)	0.0089	For each additional week in trial, the odds of completing the trial **decrease** by 2.8 %.
Period of Stability Required (weeks)	0.900	(0.814, 0.995)	0.0394	For each additional week of stability required, the odds of completing the study **decrease** by 10 %.
Standard of Care Antipsychotic Continued	11.547	(2.215, 41.472)	0.0020	For trials that allow standard of care antipsychotic to continue, the odds of completing the trial are 11.5 times **greater**.

CONCLUSIONS

The requirement of a longer trial is often necessary to ensure that complete efficacy and safety data is obtained. However, the current analysis indicates that incremental **increases in the length of an outpatient trial decrease the likelihood of subject completion**. Investigators should be aware that a longer trial may result in an increase in early termination from the study.

The **maintenance of pre-study antipsychotic also increases the odds of completion** and investigators may predict a lower drop out rate in trials that augment existing antipsychotics.

A previous analysis looking at **subject** character variables showed that **stability in Phase 1 trials increased the likelihood of completion.** In this present analysis, increasing the **required protocol length of stability decreased the likelihood of later phase completion.** A possible explanation for these discrepant results include that **participants in early phase trials are different from those in later phase trials**. Stable subjects choosing Phase 1 trials may have more investment in research independent of their present psychiatric care. Alternatively, **subjects** who present for outpatient trials and have been **stable for longer period of time may be in better systems of community care** and **may find trials** to be **burdensome** and **less necessary** to maintain stability.

The present **analysis is limited by including only 17 studies**. Only subjects from **three clinical sites** that shared Standard Operating Procedures and a subject database. The three sites also had a shared recruitment process.

The analysis is **limited by being a retrospective review**. Future prospective research across a larger number of sites and protocols may further identify what aspects of protocol design impact completion in outpatient clinical trials in subjects with Schizophrenia or Schizoaffective Disorder.

REFERENCES

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