A Retrospective Analysis of the Effects of Protocol Design on Completion Rates in Phase 1 Studies in Subjects with Stable Schizophrenia

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INTRODUCTION

Subject attrition from randomized Schizophrenia trials is a significant problem and has been found in meta-analysis to be as high as 76% (Robinowitz et al., 2005). High drop-out rates introduce selection bias, decrease the validity of intent to treat (ITT) analysis, can lead to a decrease in statistical power, and can ultimately cloud signal detection. The problem of drop-out is typically not addressed until the statistical analysis stage of the study which can decrease the validity of the results, increasing the likelihood of failed and negative trials (Levine et al, 2015).

The **impact of subject characteristics on drop-out rate has been investigated,** but recruitment is an increasing challenge in Schizophrenia trials. Adjusting study sample composition by excluding individuals with particular characteristics in an effort to prevent attrition can distort the representativeness of a sample and reduce statistical power.

Investigators have a greater degree of control over study design characteristics. Considerate study design can have a definitive, positive effect on Schizophrenia trial retention without the risks to sample size and representativeness. Previous research has determined that specific trial design characteristics can have a clear, detrimental effect on completion rate. Subject characteristics and trial design are not mutually exclusive factors. It is apparent that patient-centered trial design (i.e., designing a study in a way that is more attractive to potential subjects) improves subject satisfaction and retention (Little et al., 2012).

The authors of the present paper **study the impact of specific protocol design features on subject completion** in Phase 1 studies in subjects with stable Schizophrenia or Schizoaffective Disorder and discuss the ways that results of the present analysis can inform study design for better subject retention.

OBJECTIVES

To study the impact of protocol design on individual completion rates in Phase 1 studies in subjects with stable Schizophrenia and Schizoaffective Disorder.

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DESIGN

- The authors examine the effect **of 9 trial design** variables on subject completion in **11 Phase 1 studies** of subjects with **stable Schizophrenia or Schizoaffective Disorder**.
- The 11 trials were conducted at either of two clinical research sites (Philadelphia and Southern New Jersey) operated by PRA Health Sciences or its legacy company, CRI Lifetree.
- All studies enrolled from 2009 to 2014.
- These 11 trials enrolled **337 subjects** and had an **overall completion rate of 84%** (ranging from 75-96%).

Trial Design Variables Studied include:

1. Length of inpatient period
2. Length of outpatient period
3. Longest period between outpatient visits
4. Total study length from randomization to final visit
5. Number of outpatient visits
6. Number of arrivals to the site (total of outpatient visits and inpatient admissions)
7. Remain on or wash out of standard of care (SOC) antipsychotics
8. Placebo controlled versus no placebo
9. Administration route of the investigational product (oral versus parenteral)

Variables were analyzed via a **stepwise linear regression** analysis to assess the **predictive value of each variable** with regard to study completion (dependent variable).

RESULTS

Initially, variables were assessed for **bivariate correlation**. It was determined that the number of outpatient visits, number arrivals to the site, and the total study length were highly correlated with other variables and therefore would not be useful in the regression analysis.

Correlation Matrix of Variables

	Inpatient Length	OP Length	Longest OP	Number OP Visits	Number Arrivals	T Study Length
Inpatient Length	1	0.303	0.207	0.195	0.159	0.358
Outpatient Length	-	1	0.560	0.934	0.920	0.991
Longest OP Period	-	-	1	0.470	0.469	0.569
Number OP Visits	-	-	-	1	0.997	0.941
Number Arrivals	-	-	-	-	1	0.932
Total Study Length	-	-	-	-	-	1

Predictive Values of Variables

	Odds Ratio	95% CI	p-value	Interpretation
Inpatient Length	0.948	(0.916, 0.982)	0.0032	For each additional inpatient day, the odds of completing the study decrease by 5.2%
Outpatient Length	1.007	(1.001, 1.012)	0.0231	For each additional outpatient day, the odds of completing the study increase by 0.7%
Longest Period Between Outpatient Visits	0.947	(0.914, 0.980)	0.0020	For each additional day in the longest outpatient interval, the odds of completing the study decrease by 5.3%

- Three variables were found to have **no significant predictive value** by the stepwise regression analysis: **remain on or wash out of SOC antipsychotic, placebo controlled versus non placebo, and administration route of the investigational product**.
- Three variables were **found to have predictive value: Inpatient Length, Outpatient Length, and the Longest Period between Outpatient Visits**.

CONCLUSIONS

The requirement of inpatient stay is often necessary in early phase studies to ensure subject safety and completion of intensive procedures. However, the current analysis indicates that incremental **increases in the length of inpatient stay decrease the likelihood of subject completion**. Investigators should be aware that a longer inpatient period may result in an increase in early termination from the study.

Conversely, **lengthening the outpatient period increases the likelihood of study completion**. Investigators may consider maximizing the outpatient period to ensure study completion.

Study design that involves **greater time between outpatient visits leads to a decreased likelihood of subject completion.** During an outpatient period, consideration to more frequent on-site contact should be given to improve study completion. It is important to keep the subject engaged and for the site to remain aware of contributing factors that may impact negatively on completion (i.e., change in community treatment, non-compliance with study drug, non-compliance with study restrictions).

Investigators should **consider the impact of protocol demands on completion rates** and plan accordingly when designing protocols.

The present **analysis is limited by including only 11 studies**. Only subjects from two clinical sites that shared Standard Operating Procedures were studied. The two sites had **a high overall completion rate limiting the analysis**.

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