

## Document Coversheet

Study Title: Integrated Outpatient Treatment of Opioid Use Disorder and Severe Injection Related Infections

Institution/Site:	University of Kentucky
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## **Integrated Outpatient Treatment of Opioid Use Disorder and Severe Injection Related Infections**

**Protocol Number: 60903**

### **Statistical Analysis Plan**

All analyses will be conducted using SAS Version 9.4 (SAS Institute, Inc; Cary, NC, USA), and all hypothesis testing will be two-sided with a significance level of 0.05. P-values will be presented with 3 decimals and p-values that are less than 0.001 will be represented as <0.001.

Continuous data will be summarized using descriptive statistics: number of observations (n), arithmetic mean, standard error, minimum, and maximum. Frequencies and percentages will be used to summarize categorical (discrete) outcomes. Means and standard errors will be presented to two decimal places.

### **Analysis Populations**

One study population will be defined for analysis.

Enrolled Population - All subjects who sign the Informed Consent Form.

### **Demographics and Other Baseline Characteristics**

Demographic and baseline characteristics will be summarized descriptively and statistical tests completed (e.g., t-test, chi-square). The demographic and baseline characteristics will consist of age, sex, race, and ethnicity.

Continuous variables (age, height, weight, BMI) will be summarized by n, mean, standard deviation, min, median, and max. Frequencies and percentages will be used to describe categorical (discrete) variables including gender, race, and ethnicity.

### **Analysis of Primary Outcomes**

The primary analysis will be performed based on the Enrolled Population.

-Primary: Proportion of urine samples with negative urine drug screen for illicit opioid use

Each participant provides a urine sample for a urine drug screen at a weekly visit once discharged from the index hospitalization for their serious injection related infection (SIRI). The primary outcome will be analyzed in a generalized estimating equations (GEE) model including the treatment groups and treatment week (Zeger & Liang 1986). GEE is particularly suited for analyses of longitudinal data and allows for correlations among observations within an individual subject, for the presence of missing data, for subjects measured at different time points (i.e., weeks), and for covariates that change over time.

Within each model, subject will be treated as random effects, and the remaining parameter as fixed effects. Mixed models are suited for data with repeated measures, correlations among observations within an individual subject, and the presence of missing data. The response of individual subjects is first modeled, and then the estimates for each individual are combined in a group analysis (Singer, 1998; Ballinger 2004; Diggle et al. 1996; Gibbons et al. 1993; Kreft and De Leeuw 1998). Tukey post-hoc tests will compare active doses to placebo and other relevant active dose comparisons.

### **Analysis of Secondary Outcomes**

Secondary analyses will be performed based on the Enrolled Population. Secondary outcomes will include:

- Completion of recommended IV antibiotic therapy.
- Self-reported number of days of illicit opioid abstinence.
- Self-reported number of days of injection use of any drug.
- Number of days patients remained in buprenorphine treatment. Days retained in buprenorphine treatment will be measured through prescriptions in the prescription drug monitoring system and does not require participants to attend study visits.

Secondary analyses will be completed with Chi-square, t-tests, or Gaussian mixture model (GMM) where appropriate. Chi-square and t-tests will examine for group differences. GMM analyses will include the treatment groups and treatment week with an autoregressive symmetry (AR1) covariance structure. Within each model, subject will be treated as random effects, and the remaining parameter as fixed effects. Mixed models are suited for data with repeated measures, correlations among observations within an individual subject, and the presence of missing data. Subject will be treated as random effects and the remaining parameters fixed.

### **Safety and Tolerability Analyses**

Adverse events (AEs) recorded after signing informed consent will be included in the summary safety analysis. AEs will be summarized by treatment group and severity.

### **Missing Data**

Inspection of missing data and correlates of missingness will be examined upon study completion. The use of GEE and GMM analytic strategies obviates the need for the missing values to be imputed.

## Identification and Summary of Protocol Deviations

Major protocol deviations from the participant's entry criteria through study completion will be documented and summarized as far as they can be extracted from the numeric and coded study data.

### References:

Ballinger GA (2004) Using generalized estimating equations for longitudinal data analysis. *Organizational Research Methods* 7(2): 127-150.

Diggle PJ, Liang K, Zeger SL (1996) *Analysis of Longitudinal Data*. Oxford University Press, Inc., Oxford University Press, Inc.

Gibbons RD, Hedeker D, Elkin I, Waternaux C, Kraemer HC, Greenhouse JB, Shea MT, Imber SD, Sotsky SM, Watkins JT (1993) Some conceptual and statistical issues in analysis of longitudinal psychiatric data. Application to the NIMH treatment of Depression Collaborative Research Program dataset. *Arch Gen Psychiatry* 50: 739-50.

Kreft I, De Leeuw J (1998) *Introducing Multilevel Modeling*. Sage Publications, Ltd., Sage Publications, Ltd.

Singer JD (1998) Using SAS PROC MIXED to fit multilevel models, hierarchical models, and individual growth models. *J Educ Behav Stat* 24: 323-355.

Zeger SL, Liang K-Y, Albert P. Models for longitudinal data, a generalized estimating equation approach. *Biometrics*. 1988;44:1049-1060.