CTN-0051-A2

Treatment-as-Usual Opioid Use Outcomes Following Discharge from Detoxification and Short-Term Residential Programs Affiliated with NIDA CTN-0051

Statistical Analysis Plan (SAP)

Version 1.0
April 26, 2017

Table of Contents

Listing of Tables

Listing of Figures

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
CCC	Clinical Coordinating Center
CoC	Certificate of Confidentiality
DSC	Data and Statistics Center
DSMB	Data and Safety Monitoring Board
DHHS	Department of Health and Human Services
EDC	Electronic data capture
ERC	Ethics Review Committee
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
LN	Lead Node
MAT	Medication-assisted treatment
MDMA	Methylenedioxymethamphetamine (Ecstasy)
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
OUD	Opioid use disorder
PI	Principal Investigator
SAE	Serious adverse event
TAU	Treatment-as-usual
TLFB	Timeline Follow-Back
UDS	Urine drug screen

1.0 INTRODUCTION

1.1 Study Objective

CTN-0051-A2 (also referred to as “ancillary study”) is an observational study intended to describe opioid use amongst opioid use disorder patients following their discharge into the community from inpatient detoxification and/or short-term residential treatment programs affiliated with CTN-0051 (referred to as “parent study”).

1.2 Study Design

This is an observational study of participants with opioid use disorder leaving 5 of the detoxification and/or short-term residential units from which participants for CTN-0051 are recruited, but who are discharged to TAU in the community. Similar drug use measures but not identical are collected in this study as in CTN-0051. The goal is to estimate (1) days to first use and days to regular use, (2) number of days of use during the first four and eight weeks post-discharge to the community, and (3) number of positive, negative and missing UDSs at weeks 1, 4 and 8 post-discharge to the community.

1.3 Treatment/Intervention

There is no treatment or intervention in this study.

1.4 Database Sources

Completed forms and electronic data will be entered into the data management system in accordance with the CRF Completion Guidelines established by the DSC. Only authorized individuals shall have access to electronic CRFs.

1.5 Randomization

There is no randomization in this study.

1.6 Study Population

Approximately three hundred sixty (360) participants will be enrolled. Participants will be patients that were admitted to detoxification or short-term residential programs associated with CTN-0051 for opioid use disorder and that were discharged to the community.

1.6.1 Participant Inclusion Criteria

1. 18 years of age and older;
2. Meet DSM-5 criteria for opioid-use disorder (heroin or prescription opioids);
3. Have used opioids other than as specifically prescribed within thirty days prior to consent;
4. Seeking treatment for opioid dependence;
5. Able to provide written informed consent; and
6. Able to speak English sufficiently to understand the study procedures.

1.6.2 Participant Exclusion Criteria

1. Serious medical, psychiatric or substance use disorder that, in the opinion of the Site Principal Investigator (PI), would make participation hazardous to the participant, compromise study findings or prevent the participant from completing the study;
2. Suicidal or homicidal ideation that requires immediate attention;

3. Maintenance on methadone at doses of 30mg or greater at the time of signing consent;
4. Presence of pain of sufficient severity as to require ongoing pain management with opioids;
5. Currently in jail, prison or any inpatient overnight facility as required by court of law or have a pending legal action which may prevent an individual from completing the study;
6. If female, currently pregnant or breastfeeding or planning on conception; or
7. Prior participation in parent study CTN-0051.

1.6.3 Participant Recruitment

Participants will be recruited from the same detoxification and/or short-term residential programs participating in CTN-0051. Candidates admitted for opioid use disorder will be approached by research staff and provided information about the study.

2.0 OUTCOMES AND SUBGROUPS OF INTEREST

The outcomes are (1) days to first opioid use and days to regular use, (2) number of days of use during the first four and eight weeks post-discharge to the community, and (3) number of positive, negative, and missing UDSs at weeks 1, 4, and 8. The number of participants abstinent for four weeks and those participants who were not will also be calculated.

2.1 Timeline Follow-back (TLFB)

The Timeline Follow-back procedure was used to elicit the participant's self-reported use of substances at baseline and throughout study participation. At screening, this form was used to assess substance use for the 30-day period prior to admission to the inpatient treatment program. At Week 1, the TLFB assessed the period from discharge to the community up to the date preceding the Week 1 visit (the time in detox and/or short-term residential was not captured on this assessment). At weeks 4 and 8, the TLFB was used to assess each day since the previous TLFB assessment.

2.2 Urine Drug Screens

Urine was collected for a urine drug screen at each in-person study visit. All urine specimens were collected using FDA-approved one-step temperature-controlled urine drug test cups following all of the manufacturer's recommended procedures. The UDS tested for the presence of the following drugs: opioids, oxycodone, barbiturates, benzodiazepines, cocaine, amphetamine, methamphetamine, marijuana, methadone, and ecstasy (MDMA). Two additional single strip tests were performed: one for buprenorphine (BUP10) and a more sensitive test for opiates (OPI300). In the event urine specimen tampering was suspected, either based on the observation or the adulterant tests, study staff should have requested a second urine sample and may have observed the urine collection process according to clinic standard operating procedures.

2.3 Treatment Plans

To evaluate the outcomes, two main sub-groups from the observational cohort are (1) participants who receive any medication-assisted treatment (MAT) and (2) participants who do not receive medication-assisted treatment. Assessment of the participant's intention for treatment after discharge to community (i.e., leaving the detox and/or short-term residential unit) was assessed at the Day 0 visit (Community Discharge Plan). On the Medical Management (MM) Community Treatment form, at weeks 1, 4 and 8, participants were asked what treatment(s) he/she was engaged in, with the options being

(1) MAT with buprenorphine maintenance

(2) MAT with injectable naltrexone

(3) MAT with oral naltrexone

(4) MAT with methadone maintenance

(5) MAT with inpatient detox

(6) Psychosocial

(7) Referral to other community-based treatment

(8) Declined further treatment.

A participant will be categorized as having received any medication-assisted treatment post-discharge if at any visit (Weeks 1, 4, and 8), the treatment plan engaged in includes medication-assisted treatment.

Program type and high severity vs. low severity at baseline will also define groups to be separately analyzed. The program type subgroups will be defined based on the length of stay in the detox and/or residential facility. The date of admission to the detox unit is found on the Detoxification Utilization Summary form and the corresponding dates of discharge for both the detox unit and residential facility are found on the enrollment form. If the subject was discharged to the community from the residential facility, the total time in detox and the residential facility will be calculated. The difference between admission and discharge dates will be tabulated and categorized based on the following groupings: (1) ≤7 days, (2) 8-20 days and (3) ≥21 days.

High severity and low severity opioid use level at baseline will be defined as computed for the main CTN-0051 study stratification factor (i.e. <6 bags vs. ≥ 6 bags). To compute the opioid severity level, if the primary opioid of use in the last 7 days was not heroin or the route of administration is not IV-injection then that participant is defined as a low severity user. For IV heroin users where the quantity is not provided in bags but in dollars, bags are estimated as the dollar amount/10 rounded to the nearest integer.

All outcomes listed in Sections 5.1-5.4 will be calculated separately for each of these subgroups of the observational cohort, as well as in the overall study sample.

3.0 GENERAL CONSIDERATIONS

3.1 Terminations

All participants will be followed for the duration of the study (CTN-0051-A2) unless they withdraw consent, die, or the investigator (site PI or LI) or sponsor decides to discontinue their enrollment for any reason. Reasons for the investigator or sponsor terminating a participant from the study may include, but are not limited to, the participant becoming a threat to self or others, lack of funding, or early termination of the study by the Data and Safety Monitoring Board (DSMB) for safety or other reasons.

3.2 Sample Size and Power Calculations

3.2.1 Rationale for Sample Size and Statistical Power

No formal statistical hypothesis tests will be calculated for this study; therefore, there is neither sample size nor statistical power calculations. The study population is a convenience sample and it is anticipated that each participating site should be able to enroll approximately 60 participants for a total of approximately 360 participants. While the main objectives of this study are descriptive in nature, such as estimating the opioid use rate eight weeks after discharge to the community, it may be of interest to evaluate whether these opioid use outcomes are associated with certain covariates. Potential independent predictors of opioid use include: age, gender, race, ethnicity, use of medication-assisted treatment, and type of treatment received prior to discharge to the community.

3.2.2 Number of Sites

Five sites with inpatient detoxification programs and/or short-term residential treatment programs associated with CTN-0051 will recruit participants.

3.2.3 Projected Number of Participants per Site

Approximately 60 participants will be recruited at each of the approximately six sites.

3.2.4 Detectable Effect Sizes

Table 1 summarizes detectable effect sizes for the two outcomes: (a) time to first opioid use, and (b) time to first regular opioid use. The detectable hazard ratios (HRs) are calculated for various values of the standard deviation of the outcome measure and the overall percent of participants who had (a) used opioids or (b) regularly used opioids during the eight week follow-up period. Total sample sizes of 280, 320 and 360 were considered. If the target sample size of 360 is reached, and 60-70% of participants use or regularly use opioids by the week 8 follow-up visit, then there will be at least 80% power to detect a HR of approximately 1.46 with a type I error rate of 5%. On the other hand if only 320 participants are enrolled, then the detectable HR is around 1.50 and for 280 participants, then the detectable HR is around 1.40-1.75.

Table 1. Detectable hazard ratios for the outcomes measures time to (a) first opioid use, and (b) first regular opioid use

Total Sample Size	Detectable Hazard Ratio	Power (%)	Proportion of Participants who Used Opioids/ Regularly Used (%)	Standard Deviation of the Number of Days to First Opioid Use/Regular Use
280	1.75	83%	60%	0.4
	1.40	82%	70%	0.5
320	1.50	81%	60%	0.5
	1.47	83%	70%	0.5
360	*1.47*	*82%*	*60%*	*0.5*
	1.45	*84%*	*70%*	*0.5*

Table 2 summarizes detectable effect sizes for the outcomes based on the number of days of opioid use during the eight weeks post-discharge to the community of the study. The detectable mean differences for the two-sample *t*-test are calculated for various values of the group-specific mean and standard deviations of the outcome measure. Total sample sizes of 280, 320 and 360 were considered. If participants in one group use opioids on average two weeks out of the month, then we can detect a difference of 1.5 use days with at least 80% power (assuming a type I error rate of 5%) if the target sample size of 360 is achieved. Similarly, if participants in one group use approximately three weeks out of a month, then we can detect a difference of 1.5 days. With 320 participants enrolled, a mean difference of 1.5 days can still be detected with at least 80% power, but the detectable difference increases to 2.8 days with a total sample size of 280.

Table 2. Detectable differences in means for the number of days of opioid use during the eight weeks of follow-up

Total Sample Size*	Detectable Difference** in Means (days)	Power (%)	Mean (SD) in Group 1	Mean (SD) in Group 2
280	2.8 days	84%	14.0 (5.0)	15.8 (6.0)
	1.5 days	88%	21.0 (4.0)	22.5 (4.0)
320	1.5 days	83%	14.0 (3.5)	15.5 (5.5)
	1.5 days	83%	21.0 (3.5)	22.5 (5.5)
360	*1.5 days*	*82%*	*14.0 (3.5)*	*15.5 (6.0)*
	1.5 days	*88%*	*21.0 (4.5)*	*22.5 (4.5)*

* Assumes equal distribution of participants across the two groups.
** The difference is defined as the mean in Group 2 – mean in Group 1.

Table 3 summarizes detectable effect sizes for the outcomes based on urine drug screen testing. The detectable odds ratios are calculated for various values of the proportion of participants in each subgroup and the event rate in Group 1. Total sample sizes of 280, 320 and 360 were considered. For various values of the percent of participants in each subgroup, an odds ratio of around 2 (1.85-2.40) can be detected assuming an event rate of 50% in Group 1 with at least 80% power and total sample sizes of 280 to 360.

Table 3. Detectable odds ratios for UDS-based outcomes

Total Sample Size	Detectable Odds Ratios	Power (%)	Proportion in Group 1 (%)	Event Rate in Group 1 (%)
280	2.40	81%	20%	50%
	2.15	81%	30%	50%
	2.05	82%	40%	50%
	1.98	80%	50%	50%
	2.00	80%	60%	50%
	2.10	80%	70%	50%
	2.40	82%	80%	50%
320	2.30	82%	20%	50%
	2.05	82%	30%	50%
	1.98	83%	40%	50%
	1.90	81%	50%	50%
	1.98	84%	60%	50%
	2.00	80%	70%	50%
	2.30	84%	80%	50%
360	*2.15*	*81%*	*20%*	*50%*
	1.95	*81%*	*30%*	*50%*
	1.85	*80%*	*40%*	*50%*

Table 3. Detectable odds ratios for UDS-based outcomes				
Total Sample Size	Detectable Odds Ratios	Power (%)	Proportion in Group 1 (%)	Event Rate in Group 1 (%)
	1.85	*82%*	*50%*	*50%*
	1.85	*81%*	*60%*	*50%*
	1.95	*82%*	*70%*	*50%*
	2.15	*82%*	*80%*	*50%*

3.3 Software

All analyses will be performed utilizing SAS® version 9.3 or higher. All statistical tests will be conducted at the 5% Type I error rate (two-sided). When multiple tests are conducted, the chance of finding a significant difference in one of the tests, when in fact no difference exists, is greater than the stated Type I error rate. The investigators are aware of the multiple testing issues and will interpret results with caution and use confidence intervals where possible.

3.4 Analysis Populations

As this is an observational study, all available data will be analyzed.

3.5 Distributional Assumption Tests

Empirical distributions of all variables will be visually inspected to detect outliers. The underlying proposed statistical methods for each analysis will be examined, primarily through inspection of graphical displays, standardized residuals, or influence diagnostics. Where appropriate, transformations will be utilized or analyses will be performed utilizing a more appropriate distribution.

4.0 ANALYSES OF DEMOGRAPHIC AND BASELINE DATA

Baseline demographic variables (gender, age, race, ethnicity, educational level, employment status, and marital status) will be summarized for participants enrolled in the ancillary study. Descriptive summaries of the distribution of continuous baseline variables will be presented with percentiles (median, 25th and 75th percentiles), and with mean and standard deviation. Categorical variables will be summarized in terms of frequencies and percentages.

5.0 STATISTICAL ANALYSES

The primary objective of this study is to estimate opioid use rates, via various measures of use (Section 2), overall and separately for the sub-groups defined. Secondary exploratory analyses will involve modeling of opioid use as a function of certain independent predictors. For the primary objective all continuous variables (e.g., percent use days in the first week) will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the group-specific sample size) of observed levels will be reported for all categorical measures.

5.1 Days to First Opioid Use

The days to first opioid use will be tabulated based on the data collected on the TLFB where only illicit use is recorded. The days to first opioid use will begin being assessed on Day 0 where Day 0 is defined as the day of discharge into the community. An opioid use day is defined as use of any of the opioids reported on the TLFB including Buprenorphine, Opioid analgesics, Methadone, or Heroin. The first instance of use by self-report is defined as the first opioid use day.

5.2 Days to Regular Opioid Use

The number of days to regular use will be tabulated based on the data collected on TLFB. The days to regular use will start on Day 0 where Day 0 is defined as the day of discharge into the community. An opioid use day is defined as use of any of the opioids reported on the TLFB including Buprenorphine, Opioid analgesics, Methadone, or Heroin. The first instance of seven consecutive days of use by self-report will define the participant as a regular user. The first day of the seven consecutive days is defined as the day to regular use.

5.3 Urine Drug Screen Results

The urine drug screen (UDS) is used to assess whether the urine sample is positive for non-protocol opioids. Use for a urine sample is defined as a positive result for any of the following tests: Opiates (2000 ng), Oxycodone (OXY), Methadone (MTD), Opiates (300 ng) or Buprenorphine (BUP). UDS results are assessed at Weeks 1, 4, and 8. Illicit use only will be assessed. For example, if a subject is on a methadone treatment plan, UDS results positive for methadone will not be treated as positive UDSs.

5.4 Days of Opioid Use

The days of opioid use will be tabulated based on the data collected on the TLFB. An opioid use day is defined as use of any of the opioids reported on the TLFB including Buprenorphine, Opioid analgesics, Methadone, or Heroin.

5.5 Analysis Methods

For modeling the days to first opioid use and days to regular opioid use outcomes measures, a Cox regression model will be used after an assessment of the proportional hazards assumption. Should the key proportional hazards assumption be violated for a particular outcome and covariate, alternative models will be considered. The second set of outcomes relate to the number of days of opioid use. It is anticipated that the number of days of use will be non-normal, however we elect to analyze the data via a *t*-test which is fairly robust to misspecification of the underlying outcome distribution. Quantile regression may be used if modeling with multiple covariates is appropriate. For UDS-based outcomes, the dependent variable is binary (i.e., indicator of use or indicator of missingness) so univariate comparisons will be made using Pearson's χ^2 and any multivariate modeling will be implemented using logistic regression.

The second set of outcomes relate to the number of days of opioid use. It is anticipated that the number of days of use will be non-normal, however we elect to analyze the data via a *t*-test which is fairly robust to misspecification of the underlying outcome distribution. Quantile regression may be used if modeling with multiple covariates is appropriate. For UDS-based outcomes, the dependent variable is binary (i.e., indicator of use or indicator of missingness) so univariate comparisons will be made using Pearson's χ^2 and any multivariate modeling will be implemented using logistic regression.

5.5.1 Statistical Significance

There are no hypotheses being evaluated in this observational study with solely descriptive primary objectives, thus no formal statistical testing will be conducted. Exploratory comparisons will be made via modeling as described in Section 5.5.

5.5.2 Minority/Gender Analyses

In accordance with NIH guidelines, analyses will be completed to determine whether the outcomes of interest were significantly affected by participant minority/gender status.

6.0 MISSING DATA

The number of missing as well as the number of positive and negative UDSs will be tabulated separately when calculating the UDS outcome at baseline, and weeks 1, 4 and 8. Analyses of self-reported use time to event outcomes (e.g. time to first use) will impute intermittent missing days as use, but will not impute missing days due to drop-out or loss-to-follow-up. When tallying the days of opioid use, all missing self-reported days will be imputed as positive. The number of days imputed for each subject will also be summarized.

7.0 SAFETY ANALYSES

Since this is an observational study with no intervention, no formal safety analysis is planned. Overdoses and deaths will be tracked from the safety event reporting.

7.1.1 Adverse Events (AEs) and Serious Adverse Events (SAEs)

For purposes of this study only overdoses, whether hospitalized or not, and all deaths will be collected. At weeks 1, 4 and 8, research staff will ask about any overdoses that have occurred since the last study contact. Additionally, any deaths from any cause will be reported on the AE form. No other AEs or SAEs will be captured in the course of this observational study. Reporting definitions and procedures are outlined in the Manual of Operations.

Each of the study sites has established practices for managing medical and psychiatric emergencies, and the study staff will continue to utilize these procedures. Treatment providers at each site will be responsible for monitoring participants for possible clinical deterioration or other problems, and for implementing appropriate courses of action.

Figure 1: Diagram of Participant Enrollments

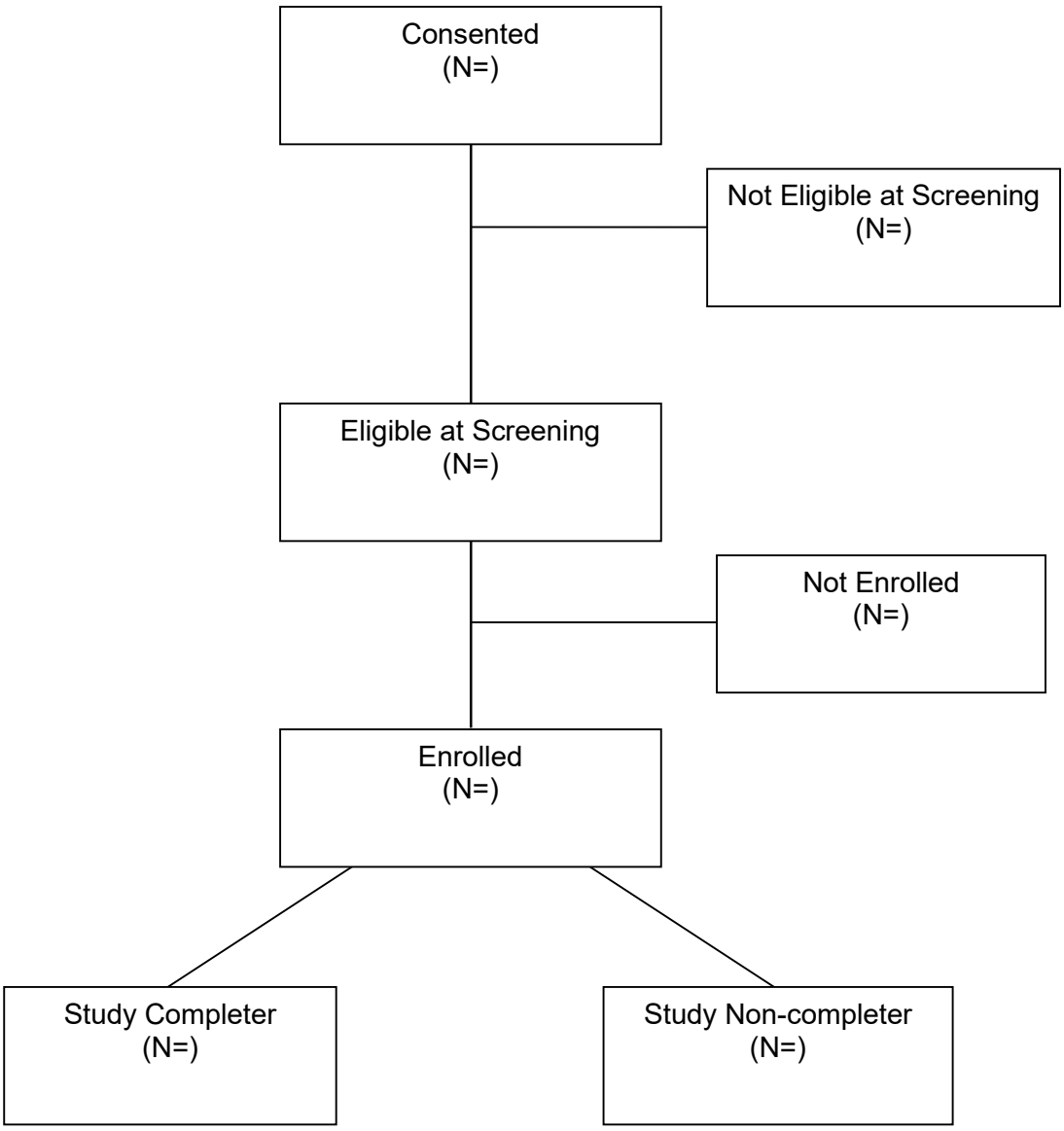


Table 1: Summary of Consents, Eligible Screens and Enrollments					
CTP	**Number of Consents**	**Number of Eligible Screens**	**Number Enrolled**	**Percent of Consents Enrolled**	**Percent of Eligible Screens Enrolled**
OV Maryhaven					
FL Gateway Community Services					
PA Tarzana Treatment Centers					
NEC Stanley Street Treatment and Resources (SSTAR)					
GNY Bellevue Hospital Center					
Total					

Table 2: Summary of Screen Failures						
	OV Maryhaven	**FL Gateway Community Services**	**PA Tarzana Treatment Centers**	**NEC Stanley Street Treatment and Resources (SSTAR)**	**GNY Bellevue Hospital Center**	**Total**
Number of consented						
Number of screen failures						
Reasons for Screen Failure* (n (%))						
18 years of age or older						
Opioid use disorder						
Opioid use past 30 days						
Seeking opioid dependence treatment						
Able to provide written informed consent						
Able to speak English/provide consent						
Severe medical, psychiatric, substance use condition						
Has suicidal or homicidal ideation						
On methadone maintenance						
Pain requiring opioid tx						
Pending legal action						
Pregnant/breastfeeding						
Participated in CTN-0051						
Participant discharged to the community						

Table 3: Summary of Participant Disposition						
	OV Maryhaven	**FL Gateway Community Services**	**PA Tarzana Treatment Centers**	**NEC Stanley Street Treatment and Resource**	**GNY Bellevue Hospital Center**	**Total**
Number of Enrolled Participants						
Number of Study Completers[1] - N (%)						
Number of Early Terminations - N (%)						

[1] Study completers are defined as participants who have completed the Week 8 visit.

Table 4: Summary of Baseline Characteristics by CTP						
Characteristic	**OV Maryhaven**	**FL Gateway Community Services**	**PA Tarzana Treatment Centers**	**NEC Stanley Street Treatment and Resource**	**GNY Bellevue Hospital Center**	**Total**
Gender						
Missing						
Male						
Female						
Participant chose not to answer						
Age (Mean(Std))						
Age						
Missing						
< 18						
18 - < 25						
25 - < 35						
35 - < 45						
45 - < 55						
55 - < 65						
65 - < 75						
75+						
Ethnicity						
Not Hispanic or Latino						
Hispanic or Latino						
Missing						
Participant chose not to answer						
Race						
Missing						
American Indian or Alaska Native						
Asian						
Black or African American						
Native Hawaiian or Pacific Islander						
White						
Other						
Multiracial						
Unknown						
Participant chose not to answer						

Table 4: Summary of Baseline Characteristics by CTP						
Characteristic	**OV Maryhaven**	**FL Gateway Community Services**	**PA Tarzana Treatment Centers**	**NEC Stanley Street Treatment and Resource**	**GNY Bellevue Hospital Center**	**Total**
Education completed						
Less than high school diploma						
High school graduate						
GED or equivalent						
Some college, no degree						
Associate's degree: occupational, technical, or vocational program						
Associate's degree: academic program						
Bachelor's degree						
Master's degree						
Professional school degree						
Doctoral degree						
Don't know						
Refused						
Marital status						
Married						
Widowed						
Divorced						
Separated						
Never married						
Living with partner						
Refused						
Don't know						
Employment						
Working now						
Only temporarily laid off, sick leave, or maternity leave						
Looking for work, unemployed						
Retired						
Disabled permanently or temporarily						
Keeping house						
Student						
Other						

Table 5: Summary of Subgroups of Interest by CTP						
Subgroups of Interest	**OV Maryhaven**	**FL Gateway Community Services**	**PA Tarzana Treatment Centers**	**NEC Stanley Street Treatment and Resource**	**GNY Bellevue Hospital Center**	**Total**
Treatment Type Received Post-Discharge						
Medication-assisted Treatment						
No Medication-assisted Treatment						
Length of Stay						
≤7 days						
8-20 days						
≥ 21 days						
Baseline Opioid Severity Level*						
Low Severity						
High Severity						
Baseline Opioid Severity Level/ Treatment Type Received Post-Discharge						
Low Severity/ Medication-assisted Treatment						
Low Severity/ No Medication-assisted Treatment						
High Severity/ Medication-assisted Treatment						
High Severity/ No Medication-assisted Treatment						
Baseline Opioid Severity Level*						
Low Severity/ ≤7 days						
Low Severity/ 8-20 days						
Low Severity/ ≥ 21 days						
High Severity/ ≤7 days						
High Severity/ 8-20 days						
High Severity/ ≥ 21 days						

* To compute the opioid severity level, if the primary opioid of use in the last 7 days was not heroin or the route of administration is not IV-injection then that participant is defined as a low severity user. For IV heroin users where the quantity is not provided in bags but in dollars, bags are estimated as the dollar amount/10 rounded to the nearest integer.

Table 6: Summary of Adverse Events by CTP						
	OV Maryhaven	**FL Gateway Community Services**	**PA Tarzana Treatment Centers**	**NEC Stanley Street Treatment and Resource**	**GNY Bellevue Hospital Center**	**Total**
Number of Enrolled Participants						
Number of Participants with Adverse Events						
Number of Adverse Events						
Adverse Event Type						
Overdose						
Overdose resulting in death						
Other death						
Severity of Adverse Event						
Grade 1-Mild						
Grade 2-Moderate						
Grade 3-Severe						
Relationship of Adverse Event						
Not Related						
Related						

Note: for the purposes of this study, only overdoses, whether hospitalized or not, and all deaths were collected

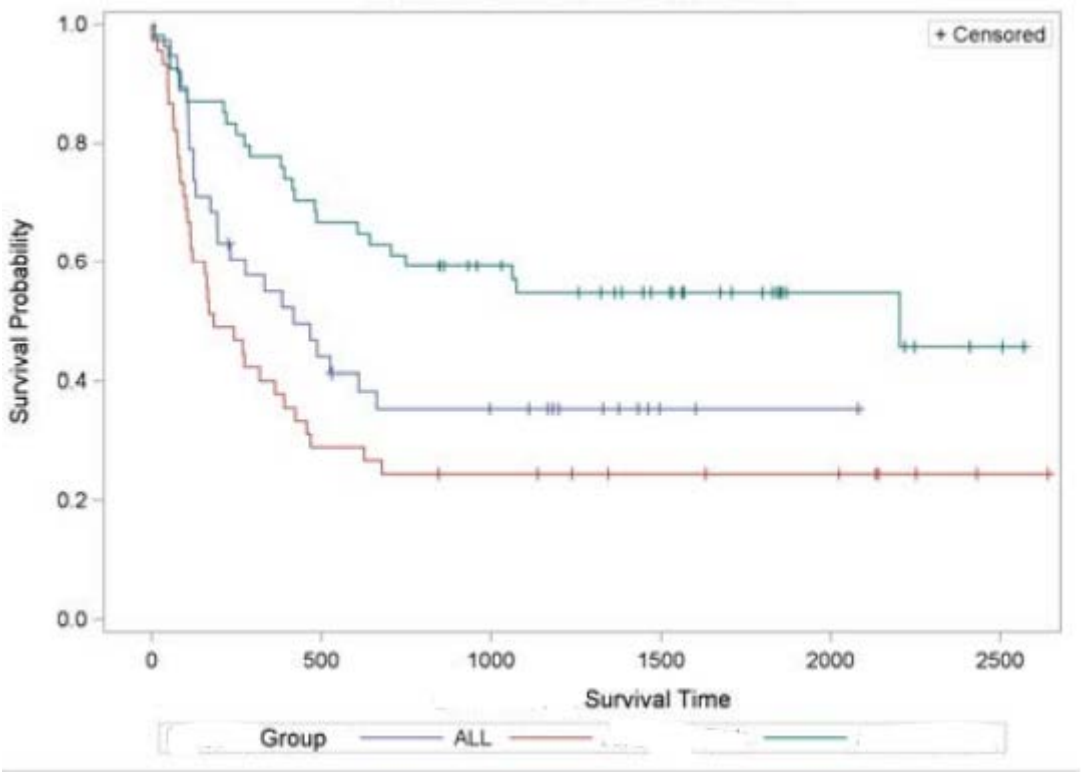
Table 7: Listing of Adverse Events by CTP								
CTP	**Participant ID**	**AE Description**	**Onset Date**	**Severity of Overdose**	**Opioids Involved**	**Primary Cause of Death**	**Aware Date**	**Hospitalization**

Table 8: Summary of Time to First Use by Type of Treatment Received Post-Discharge			
	Treatment Type Received Post-Discharge		
	Medication-assisted Treatment	**No medication-assisted Treatment**	**Total**
Number of Participants			
Any Opioid Use			
Yes			
No			
Time to First Use[2] (days)			
N			
Mean			
SD			
Median			
Min			
Max			

[2] Time to first use summary statistics are only summarized for subjects who reported any opioid use on TLFB.

Figure 2: Kaplan-Meier Plots of Time to First Use by Type of Treatment Received

Example Kaplan-Meier figure provided below.



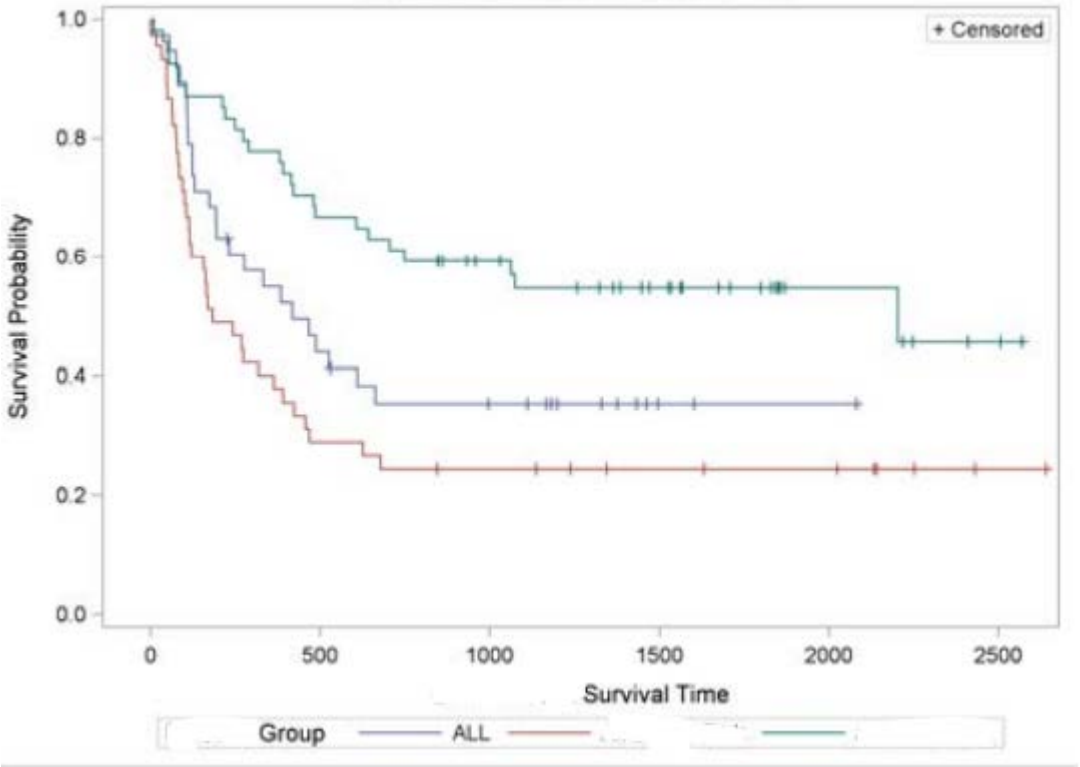
The x-axis for the Time to First Use Kaplan-Meier Plots will be measured in days. Separate curves on the same plot will be defined as the types of treatment received. Censored observations will be represented using a + sign.

Table 9: Summary of Time to First Use by Length of Stay				
	Length of Stay			
	≤7 days	**8-20 days**	**≥21 days**	**Total**
Number of Participants				
Any Opioid Use				
Yes				
No				
Time to First Use[3] (days)				
N				
Mean				
SD				
Median				
Min				
Max				

[3] Time to first use summary statistics are only summarized for subjects who reported any opioid use on TLFB.

Figure 3: Kaplan-Meier Plots of Time to First Use by Length of Stay

Example Kaplan-Meier figure provided below.



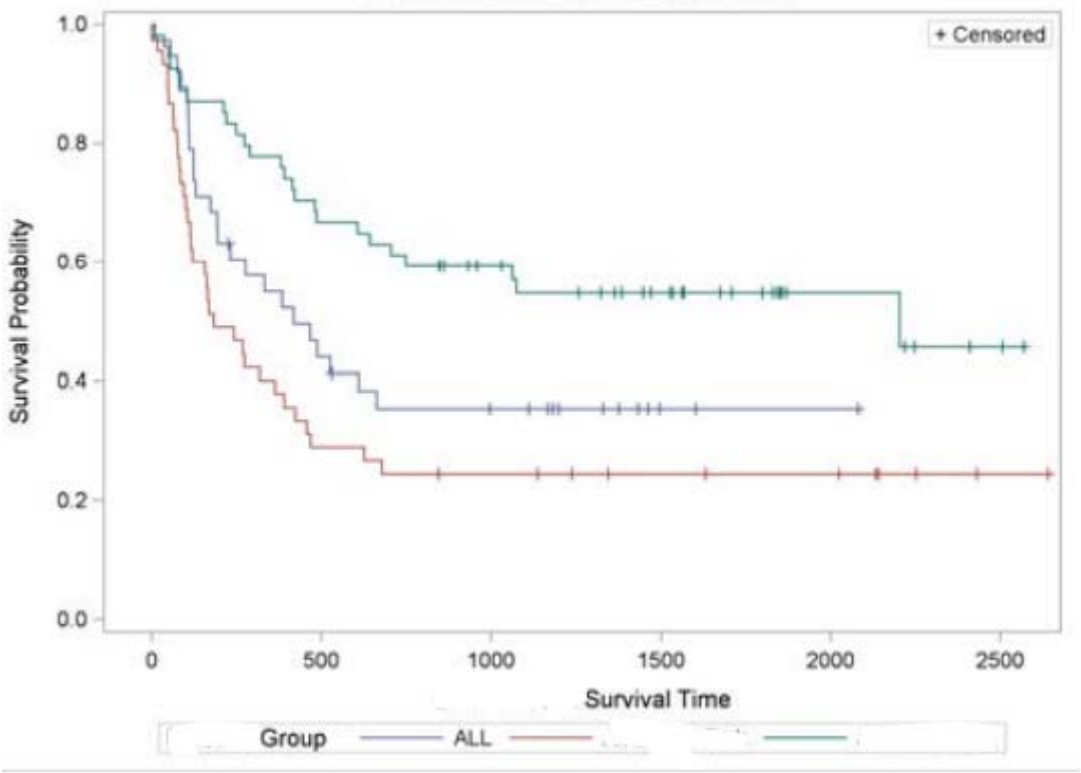
The x-axis for the Time to First Use Kaplan-Meier Plots will be measured in days. Separate curves on the same plot will be defined as the length of stay categories. Censored observations will be represented using a + sign.

Table 10: Summary of Time to First Use by Baseline Opioid Use Severity			
	Baseline Opioid Use Severity		
	Low Severity	**High Severity**	**Total**
Number of Participants			
Any Opioid Use			
Yes			
No			
Time to First Use[4] (days)			
N			
Mean			
SD			
Median			
Min			
Max			

[4] Time to first use summary statistics are only summarized for subjects who reported any opioid use on TLFB.

Figure 4: Kaplan-Meier Plots of Time to First Use by Baseline Opioid Use Severity

Example Kaplan-Meier figure provided below.



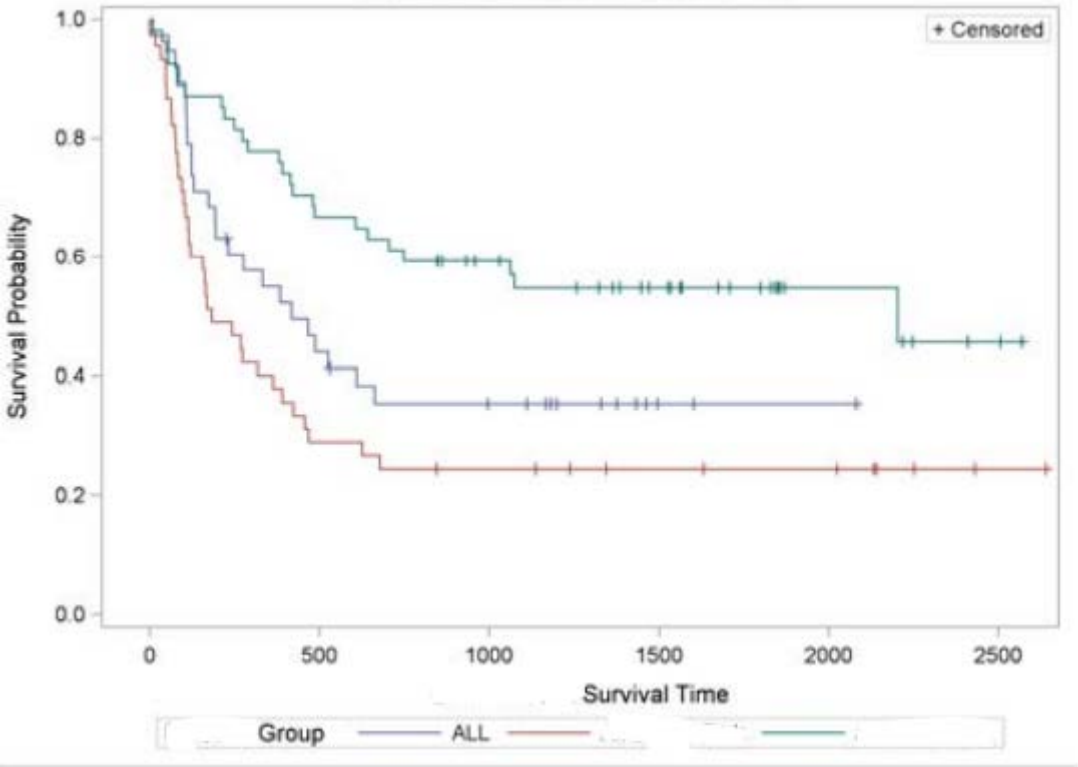
The x-axis for the Time to First Use Kaplan-Meier Plots will be measured in days. Separate curves on the same plot will be defined as the baseline opioid use severity. Censored observations will be represented using a + sign.

Table 11: Summary of Time to Regular Opioid Use[5] by Type of Treatment Received Post-Discharge			
	Treatment Type Received Post-Discharge		
	Medication-assisted Treatment	No Medication-assisted Treatment	Total
Number of Participants			
Any Regular Opioid Use			
Yes			
No			
Time to Regular Use[6] (days)			
N			
Mean			
SD			
Median			
Min			
Max			

[5] Regular use is defined as seven consecutive opioid use days as reported on TLFB.
[6] Time to regular use summary statistics are only summarized for subjects who reported any opioid use on TLFB.

Figure 5: Kaplan-Meier Plots of Time to Regular Opioid Use by Type of Treatment Received

Example Kaplan-Meier figure provided below.



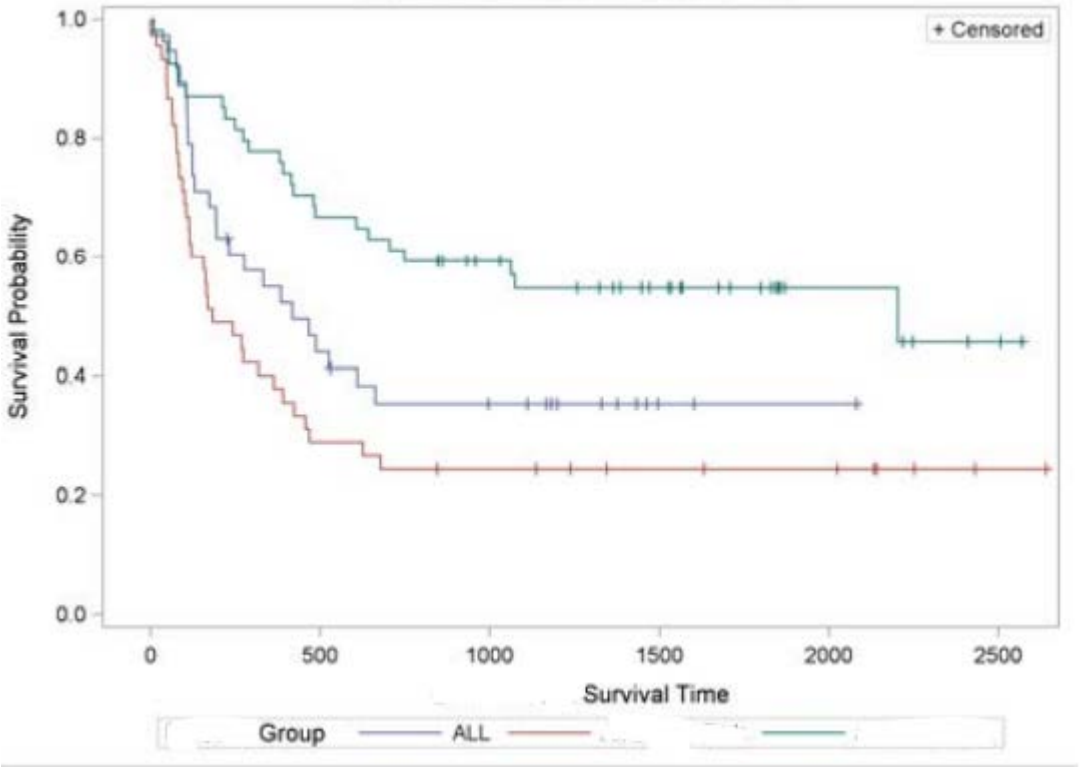
The x-axis for the Time to Regular Opioid Use Kaplan-Meier Plots will be measured in days. Separate curves on the same plot will be defined as the types of treatment received. Censored observations will be represented using a + sign.

Table 12: Summary of Time to Regular Opioid Use[7] by Length of Stay				
	Length of Stay			
	≤7 days	**8-20 days**	**≥21 days**	**Total**
Number of Participants				
Any Regular Opioid Use				
Yes				
No				
Time to Regular Use[8] (days)				
N				
Mean				
SD				
Median				
Min				
Max				

[7] Regular opioid use is defined as seven consecutive opioid use days as reported on TLFB.
[8] Time to regular use summary statistics are only summarized for subjects who reported seven consecutive opioid use days on TLFB.

Figure 6: Kaplan-Meier Plots of Time to Regular Opioid Use by Length of Stay

Example Kaplan-Meier figure provided below.



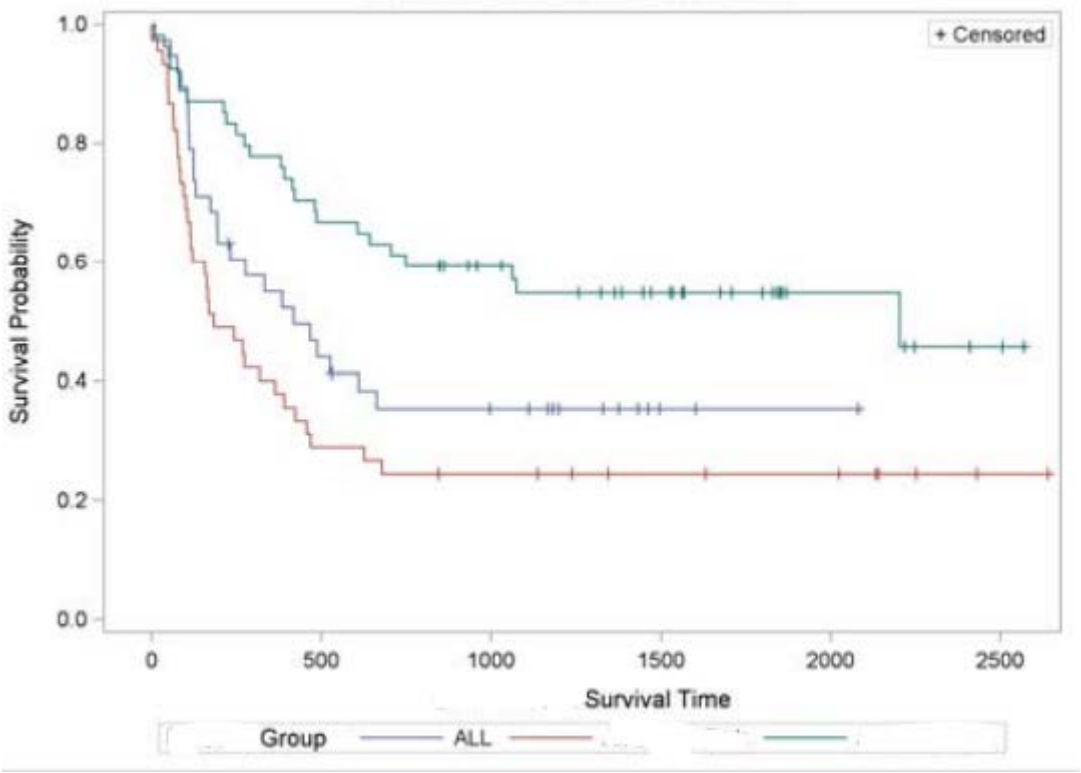
The x-axis for the Time to Regular Opioid Use Kaplan-Meier Plots will be measured in days. Separate curves on the same plot will be defined as the length of stay categories. Censored observations will be represented using a + sign.

Table 13: Summary of Time to Regular Opioid Use by Baseline Opioid Use Severity			
	Baseline Opioid Use Severity		
	Low Severity	**High Severity**	**Total**
Number of Participants			
Any Regular Opioid Use			
Yes			
No			
Time to Regular Opioid Use[9] (days)			
N			
Mean			
SD			
Median			
Min			
Max			

[9] Time to regular opioid use summary statistics are only summarized for subjects who reported seven consecutive opioid use days on TLFB.

Figure 7: Kaplan-Meier Plots of Time to Regular Opioid Use by Baseline Opioid Use Severity

Example Kaplan-Meier figure provided below.



The x-axis for the Time to Regular Opioid Use Kaplan-Meier Plots will be measured in days. Separate curves on the same plot will be defined as the baseline opioid use severity. Censored observations will be represented using a + sign.

Table 14: Summary of UDS Results by Type of Treatment Received Post-Discharge			
	Treatment Type Received Post-Discharge		
	Medication-assisted Treatment	**No Medication-assisted Treatment**	**Total**
Number of Participants			
UDS Result (Baseline[10])			
Negative			
Positive			
Missing			
UDS Result (Week 1)			
Negative			
Positive			
Missing			
UDS Result (Week 4)			
Negative			
Positive			
Missing			
UDS Result (Week 8)			
Negative			
Positive			
Missing			

[10] Day of Discharge into Community

Table 15: Summary of UDS Results by Length of Stay				
	Length of Stay			
	≤7 days	**8-20 days**	**≥21 days**	**Total**
Number of Participants				
UDS Result (Baseline[11])				
Negative				
Positive				
Missing				
UDS Result (Week 1)				
Negative				
Positive				
Missing				
UDS Result (Week 4)				
Negative				
Positive				
Missing				
UDS Result (Week 8)				
Negative				
Positive				
Missing				

[11] Day of Discharge into Community

Table 16: Summary of UDS Results by Baseline Opioid Use Severity			
	Baseline Opioid Use Severity		
	Low Severity	**High Severity**	**Total**
Number of Participants			
UDS Result (Baseline[12])			
Negative			
Positive			
Missing			
UDS Result (Week 1)			
Negative			
Positive			
Missing			
UDS Result (Week 4)			
Negative			
Positive			
Missing			
UDS Result (Week 8)			
Negative			
Positive			
Missing			

[12] Day of Discharge into Community

Table 17: Summary of Days of Opioid Use by Type of Treatment Received Post-Discharge			
	Treatment Type Received Post-Discharge		
	Medication-assisted Treatment	**No Medication-assisted Treatment**	**Total**
Number of Participants			
Days of Opioid Use[13] up to Week 1			
N			
Mean			
SD			
Median			
Min			
Max			
Subjects Abstinent up to Week 1 N(%)			
Number of Imputed Days Per Subject (up to Week 1)			
N			
Mean			
SD			
Median			
Min			
Max			
Days of Opioid Use[14] up to Week 4			
N			
Mean			
SD			
Median			
Min			
Max			
Subjects Abstinent up to Week 4 N(%)			
Number of Imputed Days Per Subject (up to Week 4)			
N			
Mean			
SD			
Median			
Min			
Max			

[13] All missing self-reported use is imputed as positive.
[14] All missing self-reported use is imputed as positive.

Table 17: Summary of Days of Opioid Use by Type of Treatment Received Post-Discharge			
	Treatment Type Received Post-Discharge		
	Medication-assisted Treatment	**No Medication-assisted Treatment**	**Total**
Days of Opioid Use[15] up to Week 8			
N			
Mean			
SD			
Median			
Min			
Max			
Subjects Abstinent up to Week 8 N(%)			
Number of Imputed Days Per Subject (up to Week 8)			
N			
Mean			
SD			
Median			
Min			
Max			

[15] All missing self-reported use is imputed as positive.

Table 18: Summary of Days of Opioid Use by Length of Stay				
	Length of Stay			
	≤7 days	**8-20 days**	**≥21 days**	**Total**
Number of Participants				
Days of Opioid Use[16] up to Week 1				
N				
Mean				
SD				
Median				
Min				
Max				
Subjects Abstinent up to Week 1 N(%)				
Number of Imputed Days Per Subject (up to Week 1)				
N				
Mean				
SD				
Median				
Min				
Max				
Days of Opioid Use[17] up to Week 4				
N				
Mean				
SD				
Median				
Min				
Max				
Subjects Abstinent up to Week 4 N(%)				
Number of Imputed Days Per Subject (up to Week 4)				
N				
Mean				
SD				
Median				
Min				
Max				

[16] All missing self-reported use is imputed as positive.
[17] All missing self-reported use is imputed as positive.

Table 18: Summary of Days of Opioid Use by Length of Stay				
	Length of Stay			
	≤7 days	**8-20 days**	**≥21 days**	**Total**
Days of Opioid Use[18] up to Week 8				
N				
Mean				
SD				
Median				
Min				
Max				
Subjects Abstinent up to Week 8 N(%)				
Number of Imputed Days Per Subject (up to Week 8)				
N				
Mean				
SD				
Median				
Min				
Max				

[18] All missing self-reported use is imputed as positive.

Table 19: Summary of Days of Opioid Use by Baseline Opioid Use Severity			
	Baseline Opioid Use Severity		
	Low Severity	**High Severity**	**Total**
Number of Participants			
Days of Opioid Use[19] up to Week 1			
N			
Mean			
SD			
Median			
Min			
Max			
Subjects Abstinent up to Week 1 N(%)			
Number of Imputed Days Per Subject (up to Week 1)			
N			
Mean			
SD			
Median			
Min			
Max			
Days of Opioid Use[20] up to Week 4			
N			
Mean			
SD			
Median			
Min			
Max			
Subjects Abstinent up to Week 4 N(%)			
Number of Imputed Days Per Subject (up to Week 4)			
N			
Mean			
SD			
Median			
Min			
Max			
Days of Opioid Use[21] up to Week 8			
N			
Mean			
SD			
Median			
Min			
Max			

[19] All missing self-reported use is imputed as positive.
[20] All missing self-reported use is imputed as positive.
[21] All missing self-reported use is imputed as positive.

Table 19: Summary of Days of Opioid Use by Baseline Opioid Use Severity			
	Baseline Opioid Use Severity		
	Low Severity	**High Severity**	**Total**
Subjects Abstinent up to Week 8 N(%)			
Number of Imputed Days Per Subject (up to Week 8)			
N			
Mean			
SD			
Median			
Min			
Max			