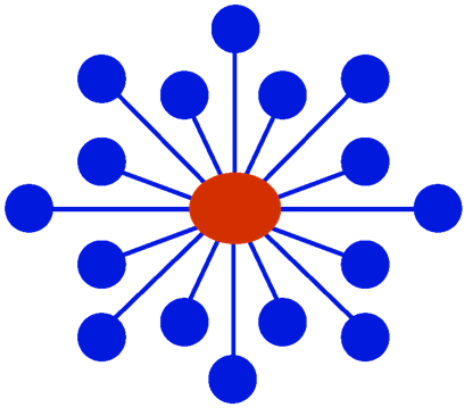

Statistical Analysis Plan for NIDA Protocol CTN-0107

Peer Intervention to Link Overdose Survivors to Treatment (PILOT)

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Version 1.0

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Prepared by:

NIDA CTN Data and Statistics Center

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LIST OF ABBREVIATIONS

BIC	Bayesian Information Criterion
CCC	Clinical Coordinating Center
CPSS	Certified Peer Support Specialist
CRF	Case Report Form
CTN	Clinical Trials Network
DSC	Data and Statistics Center
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
ED	Emergency Department
EDC	Electronic Data Capture
FAVOR	Faces and Voices of Recovery
FORCE	FAVOR Overdose Recovery Coaching Evaluation
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent form
IRB	Institutional Review Board
ITT	Intention To Treat
LI	Lead Investigator
MOUD	Medication for Opioid Use Disorder
NIDA	National Institute on Drug Abuse
NFOO	Non-fatal Overdose Involving Opioids
OHRP	Office for Human Research Protection
ORBC	Overdose Risk Behavior Checklist
OUD	Opioid Use Disorder
PILOT	Peer Intervention to Link Overdose survivors to Treatment
RA	Research Assistant
RCT	Randomized Controlled Trial
SBIRT	Screening, Brief Intervention and Referral to Treatment
SD	Standard Deviation
SUD	Substance Use Disorder
TAU	Treatment As Usual
TLFB	Timeline Follow-Back

LIST OF eCRFs

ARC	Assessment of Recovery Capital
ASU	Alcohol and Substance Use
CCJ	Crime and Criminal Justice
CLG	Contact Log
CPH	Chronic Pain History
D07	Demographics
DSM	DSM-5 Checklist
DTH	Death Form
EDH	ED Visits and Hospitalizations
EDM	ED MOUD Administration
ENRA	Enrollment 0107A
ENRC	Enrollment 0107C
ENRY	Enrollment 0107Y
ENRZ	Enrollment 0107Z
EOT	End of Treatment
FND	Fagerström Test for Nicotine Dependence
HRC	Harm Reduction Checklist
INV	Inventory - Medication and Supplies
LIF	Locator Information Form
MCA	MOUD Confirmation Assessment
MCS	MOUD Current Status
MHA	Mental Health Follow-Up Assessment
MJA	Cannabis Use Assessment
ODI	Overdose Information
ORB	Overdose Risk Behavior
PDR	Protocol Deviation Review
PDV	Protocol Deviation
PHQ	Patient Health Questionnaire (PHQ-9)
PI2	Peer Intervention Log Day 2
PI3	Peer Intervention Log Day 3
PI4	Peer Intervention Log Day 4
PI5	Peer Intervention Log Day 5
PI6	Peer Intervention Log Day 6
PI7	Peer Intervention Log Day 7
PIL	Peer Intervention Log Day 1
PSA	Prisoner Status Assessment
QLP	Quality of Life
RPN	Rolling Progress Note
RRL	Readiness Ruler

SAA	Steps Achieved Assessment
SCA	Screening Approach
SLG	Supervisor Log
STC	Study Completion
T07	Timeline Followback
TAP	TLFB Assessment Period
TS6	Treatment Satisfaction
TUH	Tobacco Use History
UDT	Urine Drug Test
V07	Visit Documentation

1.0 INTRODUCTION

The Statistical Analysis Plan (SAP) for CTN-0107 Peer Intervention to Link Overdose Survivors to Treatment (PILOT) expands upon the statistical information presented in the protocol and describes all planned analyses occurring after data lock for the primary, secondary, and safety outcome measures. The Clinical Trial Network (CTN)'s Data and Statistics Center (DSC) will conduct the analyses for the Final Study Report (FSR) as listed in Table 1 below and the Lead Node (LN) will conduct analyses as noted.

Table 1: Analysis Responsibilities

Content	Section Number	Responsible for Analysis
PARTICIPANT ENROLLMENT, DISPOSITION, AND VISIT ATTENDANCE	4.0	DSC
ANALYSIS OF PARTICIPANT BASELINE CHARACTERISTICS	5.0	DSC
ANALYSIS OF THE PRIMARY OUTCOME MEASURE	7.2	DSC
SUPPORTIVE ANALYSES OF THE PRIMARY OUTCOME MEASURE	7.3	DSC
ANALYSES OF THE SECONDARY OUTCOME MEASURES	7.5	DSC
ERROR! REFERENCE SOURCE NOT FOUND.	7.8	LN
SAFETY OUTCOMES AND ANALYSIS	8.0	DSC
DATA QUALITY	12.0	DSC

2.0 SUMMARY OF STUDY DESIGN AND PROCEDURES

2.1 Study Objectives

The primary objective of this study is to advance understanding and improve outcomes for individuals who present to an Emergency Department (ED) after surviving a non-fatal overdose involving opioids (NFOO). To achieve this objective, the study will evaluate the preliminary effectiveness of a specialized, enhanced peer recovery intervention tailored for NFOO survivors, called Peer Intervention to Link Overdose Survivors to Treatment (PILOT), on self-reported overdose risk behaviors for individuals who present to the ED after a NFOO. The PILOT intervention will be compared to treatment as usual (TAU) in the ED setting. The secondary objectives of the study are to: 1) evaluate the number of steps achieved along a modified Substance Use Disorder (SUD) Cascade of Care for individuals randomized to PILOT versus TAU, and 2) to assess whether NFOO survivors within an ED setting are willing to engage with overdose peer support using the PILOT model (feasibility).

Exploratory objectives are to assess the effects of PILOT versus TAU on the magnitude of achievement on the modified SUD Cascade of Care, on initiation of Medication for Opioid Use Disorder (MOUD), on substance use frequency, on engagement in Peer Support Services, on self-reported attendance at a recognized recovery organization or formal SUD treatment, on the percentage of toxicology screens positive for primary substance use, and on repeat non-fatal overdose and rates of death (see Section 7.7).

2.2 Study Design and Procedures

2.2.1 Study Design

This is an unblinded two-arm, multi-site, prospective, randomized controlled pilot trial comparing the effectiveness of the PILOT intervention with TAU on the frequency of self-reported overdose risk behaviors for those who survive a NFOO and present to the ED.

A total of approximately 150 eligible patients will be randomized (approximately 50 per each of 3 sites) in a 1:1 ratio to either TAU or PILOT over 12 months of recruitment. Participants will be engaged in the study for up to 210 days (7 months), which will include 180 days (6 months) of active intervention (PILOT) or TAU, and a 210-day follow-up assessment after the completion of the intervention.

2.2.2 Study Assessments

Study staff will identify eligible patients in the ED by reviewing ED trackboards, screening, and/or through ED staff identification and referral. All participants will be screened for eligibility, consented and will then complete baseline study procedures through participant interviews and a toxicology screen. Study staff will keep a weekly record of the number of patients approached for assessment of eligibility and interest in the study (SCA form).

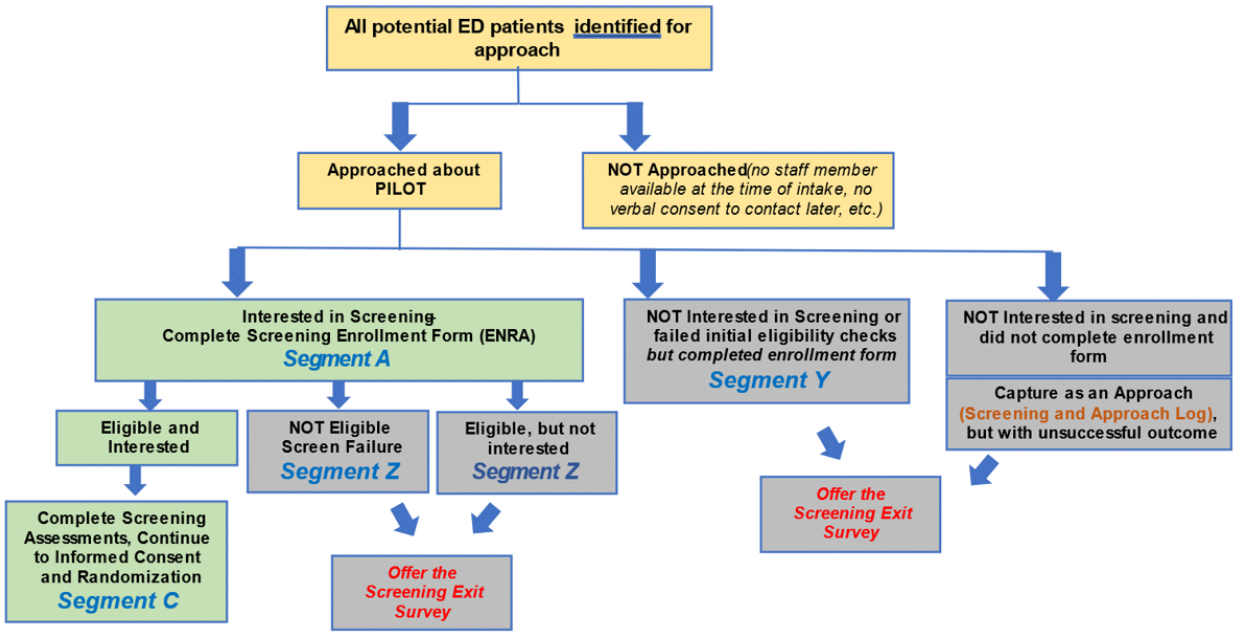
Baseline assessments will include study participant characteristics and locator information, alcohol and substance use history, past 7-day alcohol and drug use including opioids (Timeline Follow Back (TLFB) method), past year substance use and SUD diagnostic criteria (DSM-5 Checklist), overdose risk factors, and urine drug test. Other baseline assessments will include current MOUD status, readiness to change overdose risk behaviors, recovery capital, chronic pain history, tobacco use history, nicotine dependence, cannabis use, quality of life, crime and criminal justice.

Research visits will occur during the treatment period (at 30, 90, and 180 days post-randomization), and during the follow-up period (at 210 days post-randomization), with the day of randomization being considered Study Day 0. Research visits will be performed via telephone, videoconference, in person at the site, or in a community setting if the participant does not have a reliable telephone or if technology barriers exist. There will also be weekly mobile surveys sent to participants in both study arms to complete on their mobile device. Participants without mobile devices will be provided one for the duration of the study and follow-up period to complete surveys and provide a means of communication with research staff. Assessments collected at 30-, 90-, 180-, and 210-days post randomization will be similar in content to those collected at baseline (but excluding history of alcohol and substance use, chronic pain, tobacco use, and nicotine dependence and cannabis use).

Those who do not qualify for the study or decline participation will have the option to fill out a brief anonymous survey to elucidate characteristics of suspected overdose and reasons for study

decline (Screening Exit Survey). Further information on the study schema and participant flow can be found in Figure 1.

Figure 1: Schema to identify potential study participants, engage the participant, assess interest in the study, screen, and enroll study participants



2.2.3 Study Treatments

In this study, participants will be randomized to PILOT or TAU. Participants randomized to TAU will continue with routine clinical treatment in the ED. All EDs in this study will have peer support specialists operationalized in the ED for Screening, Brief Intervention, Referral to Treatment (SBIRT)-like interventions for patients presenting with substance use disorders or substance-related issues. Therefore, aside from standard ED medical treatment, TAU participants may also interact with TAU peer specialists for an SBIRT-like intervention (depending on staffing and availability). All TAU participants will be provided with referral and community resource information, consisting of at least (1) a handout providing names, locations, and telephone numbers of addiction treatment services in the area; (2) telephone access to call a clinician or facility of their choice, which will be informed by their method of healthcare coverage; and (3) information about receiving naloxone per state regulations and community resources.

Those randomized to the PILOT intervention will continue with routine clinical treatment as provided in that ED (TAU, including the TAU peer as available), but also meet with a PILOT peer – a peer with specialized training in overdose survivor engagement. The PILOT intervention will begin in the ED per the PILOT intervention manual, and PILOT participants will receive the PILOT intervention via contact with the PILOT peer over the next 180 days (6 months). Contact with the PILOT peer may occur in-person, virtually (video, telephone and/or text), or a combination. Those randomized to PILOT will also meet separately with the research staff for study assessments, including a 7-month follow-up visit after the 6-month intervention window has closed (210-day follow-up study visit).

2.2.4 Randomization

Following the collection of the assessments required for screening and eligibility, eligible participants will be randomized in a 1:1 ratio to PILOT or TAU. The randomization procedure will be conducted electronically by the DSC using a permuted block design with random block sizes and stratified by site and homelessness status. A separate randomization plan will contain additional details regarding treatment allocation.

A DSC statistician will review the randomization data on a regular basis to ensure that the scheme is being implemented according to plan. If a participant drops out of the study at any point after randomization, the randomization slot will not be re-allocated to a new participant due to the original intent-to-treat nature of the study.

2.2.5 Blinding

This study is an open-label study and thus there is no blinding to treatment assignments.

2.3 Eligibility Criteria for Selection of Study Population

Study staff will confirm self-reported overdose with potential participants, and those who confirm an NFOO meeting the criteria below will be eligible. Those who are initiated on MOUD in the ED will be included.

Non-Fatal Overdose Involving Opioids (NFOO) Description:

A person will be considered to have experienced a NFOO if he/she/they self-report affirmatively:

1. Do you think you may have experienced an overdose?

AND

2. Do you think that overdose may have involved opioids (heroin, fentanyl, or prescription pain medications such as morphine, oxycodone, or hydrocodone)?

Those who are considered to have experienced a NFOO according to answers to the questions above will be eligible for the study if the self-reported NFOO occurred in the past 30 days and other inclusion criteria are met. An overdose does not need to be confirmed for the participant to be included but should be self-reported as an overdose involving opioids by the patient to be eligible for study procedures.

2.3.1 Inclusion Criteria

Potential study participants must meet all the inclusion criteria to participate in the study:

1. Be 18 years of age or older at time of first contact by research staff (no upper age limit for inclusion).

2. Meet one of the following NFOO criteria:

    a. Having presented to the ED for any health issue within the past 48 hours AND self-report having a known or suspected overdose involving opioids in the past 72 hours,

OR

b. Having presented to the ED within the past 48 hours for any SUD-related health issue and self-report having a known or suspected overdose involving opioids in the past 30 days

3. Be able to provide sufficient locator information, defined as identifying at least two individual contacts other than the participant.

4. Be able to speak English sufficiently to understand the study procedures and provide written informed consent to participate in the study as determined by research staff.

5. Be willing and able to confirm future SUD treatment receipt as evidenced by two out of three of the following: (a) signing appropriate releases for study staff to confirm treatment with follow-up provider; (b) having technology necessary to visualize medication bottles and transmit to study team utilizing HIPAA-compliant platform; and/or (c) able and willing to undergo toxicology tests (in person or via HIPAA-compliant videoconferencing).

2.3.2 Exclusion Criteria

Individuals meeting any of the following exclusion criteria will not be eligible to participate in the study:

1. Identified as having had an intentional overdose as the Index NFOO.

2. Actively suicidal at the time of screening (defined as current intention and/or plan for suicide attempt).

3. Unable to complete study baseline procedures due to medical or psychiatric condition.

4. Currently in jail, prison or in police custody at the time of the index ED visit or under current terms of civil commitment or guardianship (i.e., OHRP-defined prisoner status).

5. Previously randomized as a participant in this study – individuals may only be enrolled and randomized once.

6. Unwilling to follow study procedures (e.g., unable to provide sufficient locator information or unavailable for follow-up assessments).

3.0 GENERAL ANALYSIS POPULATIONS, DEFINITIONS, AND CONVENTIONS

3.1 Analysis Populations

3.1.1 Preliminary Screened Population

The preliminary screened population consists of all participants who provided verbal consent and were evaluated for basic study eligibility criteria. Those found to be eligible at preliminary screening are captured under Segment A (ENRA form), whereas those not interested in participating or are ineligible and, if applicable, reasons for ineligibility, are captured under Segment Y (ENRY form).

3.1.2 Screened Population

The screened population consists of all participants who satisfied eligibility criteria during preliminary screening and were evaluated for study inclusion and exclusion criteria. All screened participants, including screen failures and reasons for failure, are captured on the ENRC form. Those screened participants who meet the criteria for study participation and provided informed consent (IC) are captured under Segment C, whereas screen failures are captured under Segment Z.

3.1.3 Intent-to-Treat Population

The Intent-to-Treat (ITT) population consists of all participants randomized to PILOT or TAU. Under ITT, these participants will be analyzed by their treatment assignment, regardless of the treatment they actually received, regardless of subsequent withdrawal from treatment or deviation from the protocol, and regardless of whether they were deemed ineligible but still randomized.

3.1.4 Safety Population

The safety population includes all participants who signed informed consent. This population will be summarized according to the actual treatment received and not necessarily to the treatment from their randomization assignment.

3.1.5 Approached Population

The approached population consists of all individuals who were approached in the ED for possible participation in the study, including those who did and did not provide verbal consent for further assessment of eligibility.

3.1.6 Per Protocol Population

The Per Protocol (PP) population is a subgroup of the ITT population and will exclude participants who received treatment different than expected based on their treatment arm (e.g., assigned to TAU but received PILOT), or otherwise deviated from the protocol in terms of intervention exposure.

3.1.7 PILOT Peer Population

The PILOT Peer population consists of all PILOT Peers who completed the two anonymous surveys on demographics and personal training history, background, and perceptions and views on recovery and harm reduction.

3.1.8 Study Completer Population

The study completer population consists of all participants who complete the Day 210 follow-up visit as indicated in Study Completion Form (STC).

3.2 General Definitions

3.2.1 Study Day

Study Day 0 is defined as the day of randomization.

3.2.2 Treatment Period

Participants will be engaged in a 180-day (6 month) treatment period of active intervention (PILOT) or TAU. Treatment period visits are scheduled for Day 30, Day 90, and Day 180. The study visit windows are inclusive and listed in Table 2.

Table 2: Study Visit Windows

Study Visit	Visit Window	
Baseline	-	Day 7
Day 30	Day 23	Day 51
Day 90	Day 76	Day 104
Day 180	Day 159	Day 194

3.2.3 Follow-up Period

After the treatment period, participants will be followed for an additional 1-month post-intervention follow up period. The follow-up period visit and assessment are scheduled for Day 210 (7 months after randomization). This study visit window closes on Day 224.

3.2.4 Baseline Value

The baseline value will be collected as part of the baseline assessment. Some baseline assessments will be administered during the index ED visit (e.g., after randomization assignment while the participant is waiting to be discharged), whereas others may be completed as post-visit activities. Change from baseline will be defined as (post-baseline value – baseline value).

3.2.5 Safety Window

The safety window for all participants enrolled in the study begins at day of signing the IC and ends at the Day 210 follow-up visit, or after the follow-up visit window lapses for participants who do not complete this final visit, or after the site confirms that a participant is permanently done with the study (e.g., participant died or withdrew consent). Safety events will be considered treatment emergent after randomization.

3.2.6 Targeted Safety Events

Given the low-risk nature of the PILOT intervention and this study, only select Adverse Events (AEs) and Serious Adverse Events (SAEs), collectively termed Targeted Safety Events, will be tracked and reported during this study. Emergency Department visits, hospitalizations, non-fatal overdoses, suicidal ideation, and deaths will be considered as targeted safety events (TSEs) in this study.

3.3 Table, Figures and Listings Conventions

Data for preliminary screened and screened populations will be summarized by site. All analyses described in the SAP for the ITT population will be summarized by randomized treatment arm (PILOT or TAU) and overall (total).

The primary outcome will be summarized by site and randomized treatment arm (PILOT or TAU). Analyses for the safety population will be summarized by randomized treatment arm (PILOT or TAU). Data quality (e.g., data audits and protocol deviations) will be summarized by site.

Continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, percentiles (median, 25th and 75th percentiles, maximum and minimum). Categorical variables will be summarized in terms of frequencies and/or percentages.

Any deviations from the above general conventions will be noted in the subsequent subsections.

4.0 PARTICIPANT ENROLLMENT, DISPOSITION, AND VISIT ATTENDANCE

4.1 Participant Enrollment

The number of preliminary screened (ENRA, ENRY) and screened participants (ENRC, ENRZ), and the corresponding reasons for ineligibility, will be summarized by site. If participants are deemed ineligible on preliminary screening or screening, they can be screened again, but are not linkable between screenings and thus will be treated as unique participants.

The trajectory of actual numbers of randomizations versus expected numbers of randomizations, according to the date each site opened for enrollment and based on a monthly expected enrollment rate of 4.17 per site, will be graphed by site and overall. Proposed versus actual randomizations will be summarized by site in a tabular fashion. The distribution of randomizations by site, strata and treatment arm will be presented.

4.2 Participant Disposition

Participants are defined as study completers if they have a Study Completion (STC) form indicating completion of the study and are considered early study terminations if they have a STC form indicating they did not complete the study. All randomized participants are expected to have an STC form. Participant disposition will be summarized by site and treatment arm for the number of participants completing the study, the number of participants terminating early from the study, and the reasons for early study termination.

The study CONSORT flow diagram will be generated (Moher, et al., 2010).

4.3 Visit Attendance

The number and percentage of participants who attend treatment period visits at Day 30, Day 90, and Day 180, and the follow-up visit at Day 210, will be presented by treatment arm and by site. Information on missed visits during the treatment period and during the follow-up period will also be presented by treatment arm and by site and will include the number of missed visits due to early study termination and during active participation, the number of participants with at least one missed visit, and the reasons for the missed visits during active participation. A visit is considered attended if the Visit Documentation form (V07) indicates that the visit was attended. The average number of missed visits per participant will be calculated by dividing the number of missed visits by the number of participants with at least one missed visit. For early study terminations, visits are only considered missed during active study participation if they were expected to occur before the early termination date.

5.0 ANALYSIS OF PARTICIPANT BASELINE CHARACTERISTICS

Baseline demographics and characteristics collected on the D07 form including sex (at birth), gender identity, age, ethnicity, race, education level, marital status, and employment status will be summarized by site and treatment arm for the ITT population. The following additional baseline characteristics will also be summarized by site and treatment arm for the ITT population: current housing status (D07 form), baseline SUD by substance (DSM form), baseline OUD by severity

(DSM form), number of baseline SUD per participant (DSM form), number of lifetime overdoses, time since last overdose (ODI form), and baseline ORBC score (ORB form). Baseline demographics and characteristics will also be summarized by treatment arm for participants who complete the study. Age will be summarized as both a continuous and categorial variable. Comparisons of randomized treatment groups with respect to baseline characteristics will be descriptive. If meaningful differences between treatments arms are suspected, statistical testing may be performed using chi-square or Fisher's exact tests for proportions and t-tests for continuous measures.

6.0 STUDY INTERVENTION ADHERENCE

6.1 Early Treatment Terminations

Participants randomized to the PILOT intervention may discontinue the study intervention (i.e., contact with a PILOT peer) prior to the Day 180 study visit, which will be entered on the End of Treatment (EOT) form. Participants who are lost to follow-up during the trial and who do not intentionally withdraw from the study or intervention, will have an EOT date consistent with when the PILOT peer made their final contact attempt. The percent of early study treatment terminations prior to the Day 180 visit and reasons for early treatment terminations will be summarized for the PILOT treatment arm by site and overall.

6.2 Treatment Exposure

PILOT peers are expected per the PILOT Peer Intervention Manual (v0.1) and training to attempt to contact participants in the active intervention PILOT treatment arm once a week at a minimum during the treatment period. More frequent contact may be needed depending on the individual participants' needs and engagement The Peer Intervention Log (PIL) form captures the intervention delivery by the PILOT peer and is expected daily until the participant reaches end of treatment. PILOT participant engagement category is assessed by the peer on the first day of each 7-day period throughout the intervention. Participants in the TAU treatment arm are not assessed for treatment exposure.

Treatment exposure will be summarized in the ITT population for the PILOT intervention arm as a) descriptive statistics for the number of contacts attempted (PIENGACT = '01') and the number of contacts completed (PIENGACT in ('01', '02')), treated as continuous variables, by site and engagement category (PICURENG), and b) the number of days of engagement by site, study period (30-day intervals), and time spent by peers engaging (PITOTLTM; categorical).

7.0 EFFICACY ANALYSIS

7.1 Definition of the Primary Outcome Measure

The primary outcome measure is the past month total score on the Overdose Risk Behavior Checklist (ORBC; ORB form), which captures the frequency of self-reported overdose risk behaviors, at Day 180. The ORBC, adapted from Bohnert et al. (2016), is a 13-item scale with 11 of the items used to generate a total score (ranging from 0-44); higher scores indicate greater frequency and number of overdose risk behaviors. The following questions on the ORB form will contribute to the total score, where a score of 0 corresponds to 'Never' and 4 to 'Very Often':

Item	Variable
1. In the past month, how often have you used illicit opioids (like heroin or fentanyl) or opioid pain medications when nobody else was around?	OROPIALN
2. In the past month, how often have you used illicit opioids (like heroin or fentanyl) or opioid pain medications in a place where you don't usually use them (in a place that you had NEVER used in before, such as a different house or apartment, or a different public space)?	OROPILOC
3. In the past month, how often did you drink alcohol within 2 hours before or after using illicit opioids (like heroin or fentanyl) or opioid pain medications?	OROPIALC
4. In the past month, how often did you take sedatives (such as Xanax or Valium) within 2 hours before or after using illicit opioids (like heroin or fentanyl) or opioid pain medications?	OROPISED
5. In the past month, how often did you use illicit opioids (like heroin or fentanyl) or opioid pain medications within 2 hours of one another?	OROPIOTH
6. In the past month, how often did you use crack or cocaine within 2 hours before or after using illicit opioids (like heroin or fentanyl) or opioid pain medications?	OROPIUPP
7. In the past month, how often did you use crystal/meth within 2 hours before or after using illicit opioids (like heroin or fentanyl) or opioid pain medications?	OROPIMET
8. In the past month, how often have you increased the amount of illicit opioids (like heroin or fentanyl) or opioid pain medications you used to more than you usually use?	ORINCUSE
9. In the past month, how often have you used illicit opioids (like heroin or fentanyl) or opioid pain medications behind a locked door?	OROPIDOR
10. In the past month, how often have you snorted any drugs?	ORSNTDRG
11. In the past month, how often have you injected any drugs?	ORINJDRG

The primary aim of this study is to compare the effectiveness of PILOT versus TAU on the primary outcome. The study hypothesis is that the PILOT intervention will result in reduced frequency of self-reported overdose risk behaviors (lower ORBC total score) at Day 180 post-randomization compared to TAU.

7.2 Analysis of the Primary Outcome Measure

The main analyses for the primary outcome will use the ITT population. A summary table of the primary outcome availability by treatment arm and site will be presented.

The primary outcome dataset will contain ORBC total scores at Day 30, Day 90, and Day 180 for each participant. ORBC data collected at supplemental visits will contribute to the primary outcome. Refusal to answer any item will result in a missing outcome measure. These data will be analyzed with a longitudinal mixed effect Poisson regression model treating the primary outcome measure ORBC total score at Day 180 as the dependent count variable. Fixed effect covariates for baseline score, treatment, study day, site, stratum, and an interaction between treatment and study day will be included. Study day will enter the model as a categorical covariate to allow greater flexibility. A random effect term for participant will be included to account for correlation of repeated measures on the same participant. The template SAS code to fit this model is given below.

```
proc glimmix data = data_prim method = quad;
        class site day strata participant;
        model risks = baseline trt|day site strata / dist = poisson link = log;
        random intercept / subject = participant;
run;
```

where:

- *data_prim* is the primary outcome dataset,
- *risks* is the ORBC total score,
- *baseline* is the participant's risk behavior score at baseline,
- *trt* is a treatment indicator with a value of 1 indicating PILOT and 0 indicating TAU,
- *day* is the study visit (Day 30, Day 90, or Day 180),
- *site is the participant's site,* and
- *strata* is the participant's stratum level.

The option *method* = *quad* indicates that the likelihood will be evaluated using the Gaussian quadrature method. Assessment of model fit will be based on standard goodness-of-fit metrics (e.g., deviance) and inspection of Pearson residuals. If the distributional assumptions are not met, other distributional assumptions will be considered and the final model will be selected according to the decision rules listed in Section 7.3.

The treatment effect of PILOT from this model will be given as a rate ratio (RR, i.e., the exponentiated estimate of the treatment x day interaction at Day 180) along with a 95% confidence interval. This can be interpreted, conditionally, as a ratio of the mean total risk behaviors score for those assigned to PILOT versus TAU at Day 180, when all other variables in the model (specifically including the baseline value) are held constant. A RR of less than 1 would indicate fewer overdose risk behaviors for those assigned to PILOT compared to those assigned to TAU. The treatment effect will be evaluated using a two-sided test with a type I error rate of 5%. A p-value of $p < 0.05$ for this RR estimate would indicate a statistically significant difference of PILOT versus TAU. Given this model is testing a single hypothesis, no adjustment for multiple testing will be performed.

The primary outcome analysis method described above, as implemented in SAS Proc GLIMMIX, excludes missing ORBC scores, but will produce approximately unbiased estimates under the assumption of missing at random (Allison, 2012). Sensitivity analyses will be done to explore rates and patterns of missingness and, where appropriate, conduct multiple imputation of missing values in order to assess the robustness of this assumption (see section 7.9).

The primary outcome availability will be summarized as ORBC scores collected by site and treatment arm at Days 30, 90, and 180. The analysis results will be summarized by treatment arm as the mean (standard deviation) of the ORBC scores at Day 180, the RR, confidence interval, and p-value.

7.3 Supportive Analyses of the Primary Outcome Measure

Key supplementary analyses will assess if PILOT resulted in a reduction of self-reported overdose risk behaviors (lower ORBC total score) at Day 30 and Day 90 compared to TAU. These analyses will utilize the same generalized linear mixed model and corresponding test for significance as for the primary outcome analysis but will focus on the rate ratios (exponentiated estimate of the treatment x day interaction) and 95% confidence intervals at Day 30 and at Day 90. Results will be summarized similar to the primary outcome.

Subgroup analyses for sex (Male, Female), age (18 – 35 years, 36 years or greater), race (Black, White, Other), ethnicity (Hispanic or Latinx, Not Hispanic or Latinx), and homelessness (homeless, not homeless) will be performed as required by the NIH (NIH, 2016). Responses of "Unknown," "Don't know" and "Refused to answer" will not be analyzed. These subgroup analyses will utilize the same generalized linear mixed model as for the primary outcome analysis, but with the inclusion of an interaction term between treatment arm and the demographic subgroup for the Day 180 timepoint. Contrasts will be used to test for statistically significant differences in the primary outcome hypothesis by subgroup.

A sensitivity analysis will examine the primary outcome with strict visit windows listed in Section 3.2.2. If the ORBC score was not collected within the visit window, it will be considered missing. This analysis will utilize the same generalized linear mixed model and corresponding test for significance as the primary outcome analysis and results will be summarized similarly.

After the proposed primary outcome analysis is performed with the Poisson regression model (Section 7.2), the following steps will be taken to assess if the distributional assumptions are met:

1. Assess the overall goodness-of-fit of the Poisson model for:
    a. over- and under-dispersion using the scaled Pearson statistic and
    b. the distribution of the residuals using Pearson residual plots.
2. If the above steps show the Poisson model deviates significantly from model assumptions, the primary outcome will then be analyzed with a negative binomial model.
3. Assess the goodness-of-fit of the negative binomial model by:
    a. repeating the goodness of fit steps above and any other necessary assessments (e.g., testing the significance of the negative binomial dispersion parameter) and
    b. comparing the Poisson and negative binomial models (e.g., AIC or likelihood ratio test)
4. If the negative binomial model deviates significantly from model assumptions, the following models may be fit and assessed:
    a. generalized Poisson
    b. zero-inflated Poisson
    c. zero-inflated negative binomial
    d. hurdle models

Whichever model is finally chosen for the outcome, the effect of treatment will be assessed with an appropriate two-sided test with a type I error rate of 0.05. In the models listed above without

zero inflation, the treatment effect is measured as RR (exponentiated estimate from the model). In models with zero inflation, the role of treatment in the proportion of zeros will be summarized, along with a RR. Site will be included in the models as a fixed effect to assess the variability in the outcome due to site and to estimate the site effect standard deviation, which also may be useful for future trials.

7.4 Definition of the Secondary Outcome Measures

The secondary outcomes of the study are: (1) number of steps achieved on a modified SUD Cascade of Care at the Day 180 visit; and (2) engagement with the study and PILOT intervention. The secondary outcome analysis will, for the Cascade of Care, focus on the count of the number of steps achieved by each participant at Day 180 (e.g., 7, out of the maximum possible 10). For engagement, the secondary outcome analysis will focus on the number of potentially eligible patients approached compared with the number willing to be enrolled, and the length of engagement and enrollment in PILOT among those willing to be enrolled and randomized to PILOT.

7.4.1 Steps Achieved on Modified SUD Cascade of Care

At Day 30, Day 90, Day 180, and Day 210 visits, participants will be asked to complete an assessment battery to assess steps achieved on the modified SUD Cascade of Care. This battery includes the Harm Reduction Checklist (HRC form), Steps Achieved Assessment (SAA form), MOUD Confirmation Assessment (MCA form), DSM-5 Checklist for Substance Use (DSM form), Urine Drug Test (UDT form), and the Assessment of Recovery Capital Scale (ARC form).

CASCADE	OD Identification & Harm Reduction	Engagement in Care		MOUD Initiation	MOUD Retention			Treatment Response & Remission (6 month)		
STEPS	1 ↑ Harm Reduction	2 Any Care	3 Regular Care	4 Any MOUD	5 MOUD X 1 mo	6 MOUD X 3 mo	7 MOUD X 6 mo	8 ↓ SUD Severity	9 Early Remission	10 ↑ Recovery Score
MEASURE	HRC	SAA		SAA	SAA and MCA			DSM and UDT		ARC

Step Eligibility: All enrolled participants will be considered to have 0 steps achieved at the time of study entry (baseline). A participant will be counted as having met a particular step if criteria are met at ANY study visit or for any length of time during the study, even if the participant subsequently does not endorse a previously endorsed item. Achievement of these steps is not necessarily sequential nor contingent upon previous steps. If data is missing for any step, it will be considered not met. That is, either evidence was previously obtained that a step was achieved, or evidence was never collected that the step was achieved.

The following will count as attaining a step:

1. Increase in Harm Reduction Exposure and Behaviors: A participant will have attained Step 1 if, on the HRC form: (1) any unchecked “achieved” box becomes checked, (2)

total score of checked boxes increases from baseline at any time during study (even if score subsequently decreases), or (3) if the Narcan availability item is checked as "Often" or "Very Often" at baseline *and* remains checked at any other study visit OR becomes checked as "Often" or "Very Often" at any visit subsequent to baseline. This assessment can be completed in person, electronically, or over the phone. A participant will be counted as having met Step 1 if the above criteria are met at ANY study visit, even if the participant subsequently does not meet the step criteria or does not endorse a previously endorsed item.

Item	Variable
Have you been provided information about safer injection practices and/or needle exchange programs?	HRSAFEIP
Have you been given a fentanyl test strip?	HRFNTTS
Have you received information about the risk of overdose with combined use of benzodiazepines (sedatives like Xanax or Ativan) and opioids?	HRINFOVD
Have you received information regarding decreased tolerance and increased risk for overdose following a period of not using drugs?	HRINFTOL
Have you received a NARCAN® kit?	HRNARKIT
If you have ever experienced depression, anxiety, or other mental health issues, did you receive information regarding treatment for mental health issues?	HRINFMHT
If you have ever experienced depression, anxiety, or other mental health issues, did you engage or are you engaging in treatment for mental health issues?	HRTRTMHT
If you have experienced serious medical problems such as problems with infections (e.g., skin, lung), liver problems (like hepatitis), breathing, did you receive information about treatment for your serious medical problems?	HRINFMED
If you have experienced serious medical problems such as problems with infections (e.g., skin, lung), liver problems (like hepatitis), breathing, did you receive or are you receiving treatment for your medical problems?	HRTRTMED
Have you been prescribed opioid painkillers (e.g., hydrocodone, oxycodone)?	HRPOPPPK

2. Engagement in care – Any: A participant will have attained Step 2 if the participant self-reports any of the following in the past month (through the SAA form): (a) scheduling a

formal SUD treatment appointment (SASCHAPT); (b) attending an in-person or on-line recovery or 12-step meeting (AA, NA, SMART, Celebrate Recovery, In the Rooms, etc.; SA12SPS2); (c) attending an in-person, virtual or phone session with a peer recovery specialist (SAPEERS2); or (d) attending at an in-person or virtual formal SUD treatment appointment (medication and/or psychosocial treatment, including outpatient, intensive outpatient or residential treatment; SAFMTRS2). Step 2 will be assessed throughout the 6-month treatment period and at the Day 210 follow-up visit. A participant will be counted as having met Step 2 (at study visits after baseline assessment) if the above criteria are met at ANY non-baseline study visit (through Day 180 visit), even if the participant subsequently does not meet the step criteria or does not endorse a previously endorsed item (i.e., any engagement in care).

3. Engagement in care – Regular: A participant will have attained Step 3 if the participant self-reports completion of any of the SAA form Step 2 b-d activities at least 3 times in the past 90 days (SA12SPS3, SAPEERS3, SAFMTRS3). A participant will be counted as having met Step 3 (after baseline assessment) if the above criteria are met for any length of time during the study, even if the participant subsequently does not meet the step criteria or does not endorse a previously endorsed item.

   If data is collected multiple times for the same visit (i.e., a form is submitted for visit number M03 and supplemental visit M03S), the data from the supplemental visit will replace any missing values for Step 3 from the original visit. The step can be achieved using data from the original or supplemental visit form.

4. Taking MOUD – Any: A participant will have attained Step 4 (after baseline assessment) if they self-report taking any dose of MOUD on the SAA form (no confirmation needed, but self-report of at least one dose; SAMOUDM1, SAMOUDM3, SAMOUDM6). A participant will be counted as having met Step 4 if the above criteria are met at ANY non-baseline study visit, even if the participant subsequently does not endorse a previously endorsed item.

5. Taking MOUD consistently over the past 30 days: A participant will have attained Step 5 if they self-report taking MOUD at least 20 of the past 30 days (SAA.SAMODDM1) AND toxicology screen(s) are positive for buprenorphine or methadone (MCA. MCMOUDSR), consistent with self-report (MCA. MCMOUDY), as confirmed at study visits.

   If (1) the participant self-reports taking naltrexone (SAA. SAVIV), or if (2) the toxicology screen(s) are negative (MCA. MCMOUDSR), unable to be obtained, or inconsistent with self-report (e.g., a participant did not take MOUD in past 10 days, but did take MOUD the previous 20 days; (MCA. MCMOUDY)), Step 5 can also be confirmed by either (a) confirmation with treatment provider (MCA. MCPRVDR) or pharmacy of prescription written and/or dispensed consistent with MOUD availability 20 of the past 30 days (MCA. MCPHARMA); OR (b) participant providing the prescription bottle at the study visit or video chat (utilizing HIPAA-compliant platform) of a prescription bottle including matching name, medication, and date dispensed consistent with MOUD availability 20 of

the past 30 days prior to the study visit (can be provided up to 90 days after the scheduled study visit; MAC. MCPPTRX). A participant will be counted as having met Step 5 (after baseline assessment) if the above criteria are met for any length of time during the study, even if the participant subsequently does not endorse a previously endorsed item.

6. Taking MOUD consistently over the past 90 days: A participant will have attained Step 6 if the participant self-reports taking MOUD at least 70 of the past 90 days (SAA form) AND toxicology screen(s) are positive for buprenorphine or methadone (MCA form), consistent with self-report. If (1) the participant self-reports taking naltrexone, or if (2) the toxicology screen is negative, unable to be obtained, or inconsistent with self-report, this step can be confirmed by either (a) confirmation with treatment provider or pharmacy of prescription written and/or dispensed consistent with MOUD availability 70 of the past 90 days; OR (b) participant providing the prescription bottle at the study visit or a video chat (utilizing HIPAA-compliant platform) of the prescription bottle including name, medication, and date dispensed consistent with MOUD availability 70 of the past 90 days (can be provided up to 90 days after the scheduled study visit). A participant will be counted as having met Step 6 if the above criteria are met for any length of time during the study, even if the participant subsequently does not endorse a previously endorsed item.

7. Taking MOUD consistently for 180 days: A participant will have attained Step 7 if the participant self-reports taking MOUD at least 150 of the past 180 days (SAA form) AND this is confirmed by either (a) confirmation with treatment provider or pharmacy; (b) providing the prescription bottle at the study visit or a video (utilizing HIPAA-compliant platform) of the prescription bottle including name, medication, and date dispensed (can be provided up to 90 days after the scheduled study visit); OR (c) 30-day + 90-day + 180-day toxicology screen positive for buprenorphine or methadone (MCA form), consistent with self-report. If (1) the participant self-reports taking naltrexone, or if (2) the toxicology screen(s) are negative, unable to be obtained, or inconsistent with self-report, this step can be confirmed by either (a) confirmation with treatment provider or pharmacy of prescription written and/or dispensed consistent with MOUD availability 150 of the past 180 days; OR (b) participant providing the prescription bottle at the study visit or a video (utilizing HIPAA-compliant platform) of the prescription bottle including name, medication, and date dispensed consistent with MOUD availability 150 of the past 180 days. Step 7 will only be available to those who are retained in the study and complete the Day 180 study visit.

8. Decrease SUD Severity: A participant will achieve Step 8 if the number of current SUD criteria met (DSM form) for the primary SUD (DSM.DSSUBUSE) decreases as compared with baseline at the Day 30, Day 90, OR Day 180 visit. A participant will be counted as having met Step 8 if the number of criteria decreases below the baseline score at ANY study visit, even if there is/was an increase in number of DSM-5 criterion met at previous or subsequent study visits.

9. Early Remission: A participant will have achieved Step 9 if the participant met 2 or more SUD criteria for any substance at baseline and subsequently meets 0-1 current SUD criteria for that substance (DSM form) AND has a toxicology screen negative for that substance at 30-day and 90-day OR 90-day and 180-day study visit (UDT form). If a participant meets criteria for more than one SUD, the participant will have met criteria for Step 9 even if remission is not achieved in each SUD identified.

10. Increase in Recovery Capital Score: A participant will have achieved Step 10 if the total score on the Assessment of Recovery Capital (ARC form) scale (Groshkova, et al.; range 0-50) increases by a value equivalent to 0.5 standard deviations within the validation sample score of 11.54 (Ward, et al.) from baseline to the 30- 90- OR 180-day visit. This equates to a 5.77 or greater point increase. A response of “agree” counts as one point. A participant will be counted as having met Step 10 if they increase above the baseline score at ANY study visit even if there is/was a decrease in ARC at previous or subsequent study visits.

If the algorithm is unclear regarding whether a specific step was achieved post-randomization, it will be adjudicated by an independent committee at the end of the trial. Should it be unclear if a specific step was achieved, the following dispute resolution will be employed. A Dispute Resolution Panel will be formed that includes 3 members. One member will be selected by the NIDA CCTN, one member will be selected by the lead team, and those two members will select a third that is independent and a context expert in opioid-related overdose. That 3-member committee will then be asked to determine if the step is met based on the definition above.

7.4.2 Engagement with the Study and PILOT Intervention

The assessment of whether recent NFOO survivors within an ED setting are willing to engage with peer support services will be measured by (a) the number of potentially eligible patients approached (Screening Approach form; SCA) compared with the number willing to be enrolled (provided verbal consent; ENRA or ENRY form), and (b) the length of engagement and enrollment in PILOT among those willing to be enrolled and randomized to PILOT. The length of engagement will be calculated from the day of randomization to the last day a PILOT participant was assessed as “Engaged” or “Partially Engaged” on the PIL form.

7.5 Analyses of the Secondary Outcome Measures

7.5.1 Steps Achieved on Modified SUD Cascade of Care

The number of steps achieved along the modified SUD Cascade of Care at Day 180 will be modeled in a similar way as the primary outcome, using a Poisson regression model with fixed effect covariates for treatment, site, and stratum. Note that no baseline score covariate is included as all participants will be considered to have achieved zero steps at baseline. The template SAS code to fit this model is given below.

```
proc glimmix data = data_sec method = quad;
        class site day strata;
        model steps = trt|day site strata / dist = poisson link = log;
        random intercept / subject = participant;
run;
```

where:

- *data_sec* is the secondary outcome dataset for the Cascade of Care,
- *steps* is the secondary outcome number of steps achieved,
- *trt* is a treatment indicator with a value of 1 indicating PILOT and 0 indicating TAU,
- *day* is the study visit (Day 30, Day 90, or Day 180),
- *site* is the participant's site, and
- *strata* is the participant's stratum level.

Assessment of model fit will be based on standard goodness-of-fit metrics (e.g., deviance), inspection of residuals; if needed, other distributional assumptions will be considered (see section 7.3).

The RR (exponentiated estimate of the treatment x day interaction at Day 180) and 95% confidence interval, with corresponding p-value from a two-sided test (type I error rate of 5%), from this model will be used to assess the effect and significance of PILOT as compared to TAU for this secondary outcome. Given this model is testing a single hypothesis, no adjustment for multiple testing will be performed.

It is possible that participants entering the trial may not have a primary diagnosis of OUD, or even SUD and, as a result, be ineligible at baseline for some steps in the SUD Cascade of Care. However, during the study a participant may endorse OUD, or some SUD, even if none were endorsed at baseline, and become eligible for these steps. The assumption made here for the prespecified analysis is that of protection/balance by randomization. That is, participants entering without OUD, or without SUD, are likely to be balanced between treatment groups due to random assignment, such that any effects would be equal between PILOT and TAU. This assumption will be assessed by comparing the frequency distribution of participants with no identified OUD or SUD at baseline (as determined via administration of the DSM-5 checklist), between treatment arms.

7.5.2 Engagement with the Study and PILOT Intervention

For engagement with the study and with the PILOT intervention, the number of participants approached (from SCA form) and number who were willing to engage with PILOT peers, as well as the percent of those approached who were willing to engage, will be summarized. A 95% confidence interval will be provided for this percent. The length of engagement with PILOT will be similarly summarized. The template SAS code for these two analyses is given below:

```
proc freq data = secondout_consented;
  tables consented / binomial(level = 'Yes' CL = wald);
  weight count;
run;
```

where:

- *secondout_consented* is the summarized dataset containing numbers of participants who provided or did not provide written informed consent to participate,
- *consented* is a categorical variable which has "Yes" and "No" responses, with "Yes" being consented to participate in the study (EC0107A.S07CNSNT or EC0107Y.S07CNSNT), and

- *count* is the number of participants who provided the corresponding response, out of patients approached for the study (SCA.SCNPTAPR).

This analysis generates the binomial proportion (with Wald confidence limits) for those consenting to be in the study.

```
proc means data = secondout_length mean std p25 p50 p75 min max clm;
   var length;
run;
```

where:

- *secondout_length* is the dataset containing for each participant in PILOT treatment arm the days since randomization for each peer intervention,
- *length* is the number of days between the randomization date and the last intervention for that participant, as indicated on the PIL form in PILOT treatment arm (PIL.PIENGACT, PI2.P2ENGACT, …, PI7.P7ENGACT).

This analysis generates descriptive summary statistics (mean, standard deviation, quantiles, and range) for the duration of engagement in the PILOT intervention.

7.6 Supportive Analyses of the Secondary Outcome Measures

Acknowledging that individuals may vary in presence and types of SUD diagnoses, additional supportive analyses will be done to evaluate the differing numbers of steps achieved along the modified SUD Cascade of Care for each sub-group of enrolled participants: primary OUD, primary SUD other than OUD, and no identified SUD at baseline (as determined via administration of the DSM-5 checklist). These subgroup analyses will utilize the same Poisson regression model as for the prespecified secondary outcome analysis, but with the inclusion of an interaction term between treatment and subgroup. Contrasts will be used to test for statistically significant differences in the secondary outcome (number of steps achieved) by subgroup.

7.7 Definition of the Exploratory Outcome Measures

1. Exploratory Aim 1: To assess the effects of PILOT versus TAU on the achievement (yes/no) and magnitude of achievement (e.g., improvement in Addiction Recovery Capital Scale by 3 points, number of steps achieved) on the modified SUD Cascade of Care.

2. Exploratory Aim 2: To evaluate the effectiveness of PILOT versus TAU on initiation of MOUD in the ED (EDM) for those with any level of OUD at baseline (DSM; assessed via self-report upon ED discharge or in follow-up assessment if unable to be assessed at ED discharge).

3. Exploratory Aim 3: To assess the effects of PILOT versus TAU on substance use frequency at 30, 90, and 180 days via self-reported days of illicit opioid use measured by Timeline Follow-Back (TLFB).

4. Exploratory Aim 4: To evaluate the degree of engagement in Peer Support Services in those randomized to PILOT versus TAU at 30, 90, and 180 days, measured as the number of contacts received or initiated with a Peer Support Specialist in the past month (PIL; phone, video, or in-person).

5. Exploratory Aim 5: To evaluate the effectiveness of PILOT versus TAU on self-reported attendance in 12-step meetings, peer support services, other recognized recovery organization, or formal SUD treatment at any time point during enrollment, defined as self-report of having attended a meeting or appointment (SAA; phone, video, or in-person).

6. Exploratory Aim 6: To evaluate the effectiveness of PILOT versus TAU on the percentage of urine toxicology screens (UDT) positive for primary substance of use (as per DSM-5 Checklist: opioids, alcohol, amphetamines, cannabis, cocaine, or sedatives) at 30-, 90-, 180-, and 210-days post-randomization.

7. Exploratory Aim 7: To evaluate the effectiveness of PILOT versus TAU on repeat non-fatal overdose (ODI) and 210-day rates of death (DTH; all-cause mortality), including death by overdose.

7.8 Analyses of the Exploratory Outcome Measures

The following are the planned statistical analysis methods for the specified exploratory objectives. However, given the exploratory nature of these, the actual analysis methods may differ from the proposed methods given below.

1. Each step on the modified SUD Cascade of Care will be treated as a binary outcome. A separate logistic regression model will be fit to each with at least a treatment covariate. The effect of PILOT as compared to TAU will be measured by an odds ratio (OR). The OR will be reported, along with 95% confidence interval and p-value, for each step. This process will be repeated for the 30-, 90-, and 180-day outcomes.

2. Initiation for medications for OUD in the ED, among those participants with OUD, will be summarized by frequencies and percentages in each treatment arm. The effect of PILOT compared to TAU will be measured by an OR with 95% confidence interval. A Chi-squared test will be performed.

3. Number of days of self-reported frequency of use in the past 7 days will be summarized by treatment arm. A hypothesis test analogous to the primary outcome will be conducted.

4. The number of meaningful contacts with a PILOT peer in the past month will be summarized by treatment arm. Similar to the primary outcome, the effect will be measured by a RR with 95% confidence interval. A hypothesis test analogous to the primary outcome will be conducted.

5. Self-reported attendance in a 12-step meeting, peer support services, other recognized recovery organization, or formal SUD treatment at any time during study participation will be summarized by frequency and percentages in each treatment arm. The effect of PILOT as compared to TAU will be measured by an OR with 95% confidence interval. A Chi-squared test will be performed.

6. The percent of urine toxicology screens positive for primary substance of use will be summarized by proportion greater than 0% and continuous descriptive statistics for the proportion positive by treatment arm.

7. Occurrence of a non-fatal overdose at any time during study participations will be summarized by frequencies and percentages. The effect of PILOT as compared to TAU will be measured by an OR with 95% confidence interval. A Chi-squared test will be

performed. The same process will be done for all-cause mortality and death by overdose. In the event of likely dropout, time-to-event analyses may need to be performed instead. In such cases, simple Kaplan-Meier plots will be given with associated log-rank tests on the effect of PILOT as compared to TAU. Cox proportional hazards regression models may be considered as well. All-cause mortality or death by overdose may present a competing risk for non-fatal overdose. Causes of death different from overdose (that is, those with an all-cause mortality that are not overdose) may present a competing risk for death by overdose as well. As such, appropriate Fine and Gray models will be considered.

The exploratory objectives will be tested as applicable, with two-sided tests and with a type I error rate of 0.05. No attempt will be made to adjust for multiple comparisons within the exploratory objectives.

7.9 Missing Data Analysis

The prespecified primary outcome analysis method takes into account all available data for a participant, thereby minimizing the impact of missing values. Nevertheless, this analysis assumes that missing values are missing at random (MAR); a series of sensitivity analyses will be done to assess this assumption and the impact of missing data on the results of the primary outcome analysis.

Following standard guidance (European Medicines Agency, 2011; NIH, 2016), rates and patterns (e.g., dropout versus intermittent) of missing ORBC scores and reasons for missingness (V07 form) will be summarized by treatment arm and site to assess possible missing data mechanisms. Probability of missingness will be assessed in relation to other variables, including age, ethnicity, race, education level, marital status, employment status, and homelessness, using logistic regression. Template SAS code for examining patterns of missingness is given below:

```
proc mi data = data_miss nimpute = 0;
        var day30 - day180 trt site;
        ods output miss_pattern = pattern;
run;
```

where:

- *data_miss* is the dataset with ORCB scores (or missing values) for each treatment period visit, arranged in wide format with one row per participant,
- *day30 – day180* are the variables indicating ORBC total scores (or missing values) at Day 30, Day 90, and Day 180,
- *trt* is a treatment indicator with a value of 1 indicating PILOT and 0 indicating TAU, and
- *site* is the variable corresponding to the participant's site level.

Mechanisms of missingness cannot be concluded from observed data alone (i.e., the similarity of missing and observed values can never be evaluated). However, sensitivity analyses will be done to compare different assumptions of missingness in order to assess the robustness of conclusions from the primary outcome analysis. Considering the possibility that ORBC values may be missing not at random (MNAR), multiple imputation utilizing pattern mixture models will be performed (Ratitch, 2013). Under this approach, missing values are imputed using plausible scenarios of MNAR and, if resulting in different conclusions from MAR, may suggest that the MAR assumption of the primary outcome analysis is not robust. Multiple imputation will be performed in SAS using

Proc MI (Yuan, 2011). Imputation under the MNAR assumption will consider scenarios of missing values that have a systematically poorer outcome compared to non-missing values in the PILOT treatment arm. This analysis will quantify how much poorer (i.e., higher average ORBC total scores) missing values would need to be in order to qualitatively change the conclusions of the primary outcome analysis.

By definition, the secondary outcome measure number of steps achieved on the modified SUD Cascade of Care will have no missing data. A step is only considered attained if sufficient information is gathered by the assessment battery to meet the criteria for achievement (section 7.4.1), otherwise the step is considered not attained. No missing data handling methods are planned for the other secondary and exploratory outcomes.

8.0 SAFETY OUTCOMES AND ANALYSIS

Safety outcomes include hospitalizations, ED visits, non-fatal overdoses, and suicidal ideation, and death.

8.1 Hospitalizations

Treatment period and follow-up period hospitalizations will be summarized by treatment arm. The number of participants with at least one hospitalization, number of participants with at least one hospitalization related to substance use, and number of hospitalizations per participant will be presented by treatment arm. A listing of hospitalizations by treatment arm will be generated. The listing will include Site, Participant ID, date of enrollment, date of hospitalization, discharge date, primary, secondary, and tertiary diagnosis/complaint, severity, and outcome. Hospitalizations are captured on the ED Visits and Hospitalization (EDH) form.

8.2 Emergency Department Visits

Treatment period and follow-up period ED visits will be summarized by treatment arm. The number of participants with at least one ED visit, number of participants with at least one ED visit related to substance use, and number of ED visits per participant will be presented by treatment arm. A listing of ED visits by treatment arm will be generated. The listing will include Site, Participant ID, date of enrollment, date of ED visit, discharge date, primary, secondary, and tertiary diagnosis/complaint, severity, and outcome. ED visits are captured on the ED Visits and Hospitalization (EDH) form.

8.3 Overdoses

A summary table will be provided with the number of non-fatal opioid overdoses by treatment arm and by study visit (Baseline, Day 30, Day 90, Day 180, and Day 210 follow-up visit) as captured on the Overdose Information (ODI) form. At the baseline visit, participants are asked about overdoses in the past 30 days. At Day 30, Day 90, Day 180, and Day 210 follow-up visits, participants are asked about overdoses since the last study visit. The number of overdoses where NARCAN (naloxone) was used to reverse overdose, overdoses that resulted in treatment at an ED, and overdoses that resulted in being admitted to the hospital will also be summarized by treatment arm, of the two most recent overdoses per participant per visit. The number of participants with at least one opioid overdose and the number of opioid overdoses per participant (including participants experiencing no opioid overdoses) will also be summarized by treatment arm. A detailed listing of non-fatal opioid overdoses by treatment arm will be provided. The listing will include Site, Participant ID, date of enrollment, visit, date of assessment, number of overdoses, and comments from the Overdose Information (ODI) form.

8.4 Suicide Risk

The suicide risk will be summarized by treatment arm and study visit based on the responses given to the question 'Over the last 2 weeks, how often have you been bothered by any of the following problems? Thoughts that you would be better off dead or of hurting yourself in some way?', asked as a part of the 9-item version of the Patient Health Questionnaire (PHQ-9). A participant is considered to have endorsed suicidality if they indicate several days, more than half the days, or nearly every day having thoughts they are better off dead or of hurting themselves. A listing of visits for participants who endorse suicidality at any visit will be provided by treatment arm. The listing will include Site, Participant ID, date of enrollment, visit, date of assessment, and response to the question 'Over the last two weeks, how often have you been bothered by thoughts that you would be better off dead, or of hurting yourself in some way?' (PHQ-9 form).

8.5 Death

A listing of deaths will be provided by treatment arm (DTH form). The listing will include Site, Participant ID, date of enrollment, date of death, source of death report, primary, secondary, and tertiary cause of death, and MedDRA® coded preferred term and system organ class. Narratives of deaths will also be provided.

9.0 SIGNIFICANCE TESTING AND MULTIPLICITY

The primary and secondary outcomes will be evaluated using two-sided tests with a type I error rate of 0.05. No attempt will be made to adjust for multiple testing on the primary and secondary outcomes as, in both cases, inference is focused on a single hypothesis test.

The exploratory objectives will be tested as applicable, with a two-sided test and with a type I error rate of 0.05. No attempt will be made to adjust for multiple comparisons within the exploratory objectives.

10.0 SAMPLE SIZE AND POWER

Power analyses and sample size calculation were performed with respect to the first specific aim of the primary objective: comparing PILOT to TAU on the basis of the frequency of self-reported overdose risk behaviors at 180 days. This was conducted via simulation. The simulations required specifying the data generating/simulation process and a hypothesis test.

The self-reported overdose risk behaviors to be used for this trial are modified and expanded from one used by (Bohnert, et al., 2016). In their version, the maximum score was 32 and they found an average of 3.3 and 3.8 in their control and intervention groups, respectively, at baseline. They used a Poisson regression model to assess their intervention effect. Their estimated intervention effect was a 0.72 rate ratio (RR). To this end, for the power simulations presented here, a mean of 3.55 was considered, with a treatment effect of 0.72. For each (simulated) participant, a baseline score was generated from a Poisson distribution with a mean, or λ value, of 3.55. As a Poisson regression model with covariates for baseline score, treatment, site, and stratum will be used for power simulation purposes, coefficients for each must be specified for the simulation. The coefficients for site and stratum were set to 0 to specify no effect of either. Bohnert, et al. (2016) reported a coefficient of approximately 0.068, $\ln(1.07)$, for the baseline score coefficient, which will also be used here. The intercept was set as approximately 1.03, from setting $\ln(\lambda) = \beta_0 + \ln(1.07) \times baseline$ and solving for β_0 (assuming both λ and $baseline$ are 3.55 to match the TAU case). The post-treatment outcome value for those assigned to TAU was generated from a Poisson distribution with a mean of $\exp(1.03 + \ln(1.07) \times baseline)$, where $baseline$ was their

generated baseline score. For participants assigned to PILOT, their post-treatment outcome value was generated from a Poisson distribution with a mean of $\exp(1.03 + \ln(1.07) \times baseline + \ln(0.72))$, to achieve the desired 0.72 RR for the same baseline values. Site (3 levels) and stratum (2 levels) were also generated for each participant but, again, had no effect on the outcome.

After data was simulated, a Poisson regression model was fit with fixed effects for baseline score, treatment, site, and strata. Treatment was declared significant if the p-value for the treatment coefficient was strictly less than 0.05. The entire process was repeated 10,000 times. The proportion of times the treatment was significant is an estimate of the power for the scenario.
To assess the sensitivity of the results to the assumptions made, differing values for the specified simulation parameters were also considered. Specifically, values of 2.8, 3.3, 3.8, and 4.3 were considered in place of the 3.55 mean at baseline. Given that this trial will use an expanded version of the risk behaviors used in Bohnert, et al. (2016), it would be reasonable to guess that the mean frequency at baseline for this trial would higher. However, a higher value actually (as will be shown) increases power, so the 3.55 mean used here can be viewed as conservative. Larger values of 5, 10, 15, 20, 25 were also used to clearly show this pattern. Also considered were different values of the RR: 0.70, 0.74, 0.76, 0.78, and 0.80. Note that values closer to 1 are weaker effects and would thus have lower power with all other settings fixed.

Results are presented in the table and two figures below. With a mean of 3.55 at baseline and a RR of 3.55, there is over 90% power to detect the difference with a sample size of 150. There is over 80% power with a lower sample size of 100 as well. Power increases as the mean at baseline increases, as shown by Table 2 and the Power Results by Mean at Baseline figure. At a mean at baseline of as low as 2.8, there is still over 85% power to detect a RR of 0.72 with a sample size of 150. Power also increased as the RR decreased. With a sample size of 150 and a mean at baseline of 3.55, there is over 80% power to detect a difference of up to 0.76. The initial estimate of a 0.72 RR by Bohnert, et al. (2016) came from data on participants who possibly did not experience an overdose. Their estimate of RR in just the group experiencing an overdose was 0.65. Their intervention also consisted of just a 30-minute motivation interview session by a therapist, along with control procedures, as compared to peer mentorship that will be used in this trial. So, while the simulation results here are sensitive to changes in treatment effect (RR), there is reason to believe the value of 0.72 used is conservative. For these reasons (greater than 90% power at specified parameters, relative robustness to their specification), a sample size of 150 is justified for this trial.

10.1 Table 2: Power Results

		Total Sample Size		
Mean Score at Baseline	**Rate Ratio**	**100**	**125**	**150**
2.8	0.70	75.99%	85.48%	91.00%
	0.72	69.31%	79.20%	86.92%
	0.74	63.02%	73.39%	80.73%
	0.76	54.99%	65.55%	74.58%
	0.78	47.62%	57.87%	66.25%
	0.80	40.90%	49.40%	56.61%

		Total Sample Size		
Mean Score at Baseline	**Rate Ratio**	**100**	**125**	**150**
3.3	0.70	82.99%	90.65%	95.14%
	0.72	76.74%	85.59%	91.56%
	0.74	70.58%	80.35%	86.68%
	0.76	62.24%	72.37%	80.79%
	0.78	54.51%	65.21%	73.33%
	0.80	46.46%	56.24%	63.67%
3.55	0.70	85.48%	92.75%	96.15%
	0.72	80.08%	88.34%	93.32%
	0.74	73.70%	82.60%	89.23%
	0.76	65.15%	76.12%	83.57%
	0.78	58.49%	67.16%	76.19%
	0.80	49.38%	59.03%	67.69%
3.8	0.70	88.40%	93.99%	97.42%
	0.72	82.30%	90.18%	94.83%
	0.74	76.37%	85.09%	90.98%
	0.76	68.74%	78.61%	85.65%
	0.78	60.08%	71.62%	78.76%
	0.80	52.01%	61.83%	69.92%
4.3	0.70	91.46%	96.19%	98.46%
	0.72	86.85%	93.33%	96.79%
	0.74	81.08%	89.28%	93.58%
	0.76	73.69%	83.15%	89.91%
	0.78	65.87%	75.77%	83.44%
	0.80	57.54%	67.32%	75.98%

Figure 2: Power Results by RR

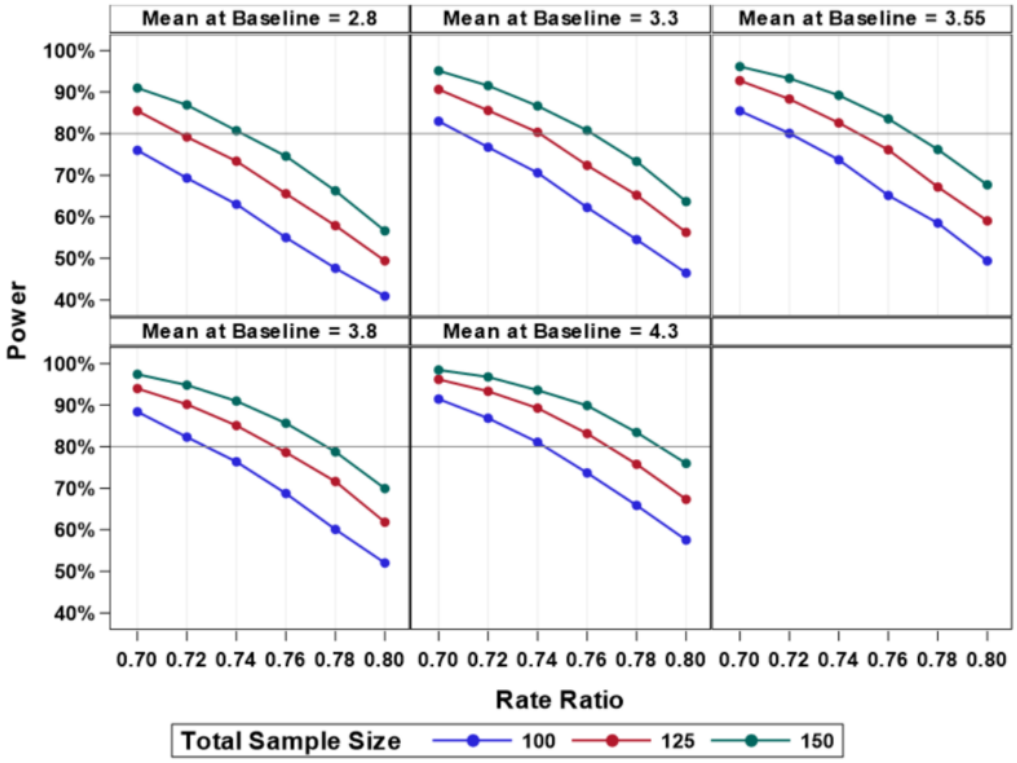
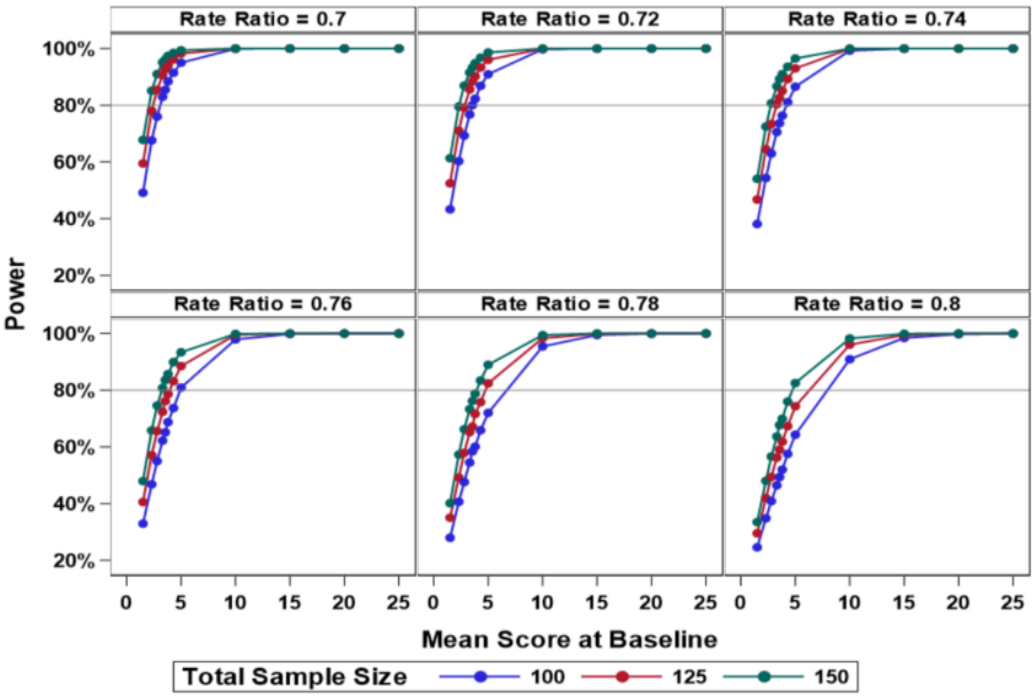


Figure 3: Power Results by Mean at Baseline



11.0 INTERIM ANALYSES AND DATA MONITORING

Enrollment, safety and data quality reports will be prepared for the Data and Safety Monitoring Board (DSMB), and they may request interim analyses at any time during the trial. No interim analyses relating to futility or sample size re-estimation will be implemented in this pilot study.

11.1 Safety Interim Analyses

Safety interim looks will be performed for the regular DSMB meetings or at unscheduled times per DSMB request. These will include descriptive analyses of TSEs (ED visits, hospitalizations, non-fatal overdoses, and suicidal ideation). Listing of death events will include the following: system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) codes; primary and secondary causes of death; and whether the death had drug or alcohol-related contributing factors (even if not listed as primary cause of death).

12.0 DATA QUALITY

12.1 Data Audits

A summary of data audit results from site interim monitoring visits conducted by CCC monitors will be presented by site, including date of audit, total fields audited, total data discrepancies, and error rate.

12.2 Protocol Deviations

Protocol deviations will be summarized by site and will include the number of deviations reported, the number of participants each deviation affects, frequencies for the types of protocol deviations, and information on whether the protocol deviation was deemed minor or major. A detailed listing of protocol deviations by deviation category will be provided. The listing will include site, participant ID, date of protocol deviation, date protocol deviation entered in EDC (Electronic Data Capture), deviation type, reason for protocol deviation, relatedness to COVID-19, deviation description, corrective action to be taken, plan to prevent recurrence, IRB reporting required, IRB notification at continuing review, and planned or actual IRB report date.

13.0 SOFTWARE TO BE USED FOR ANALYSES

All analyses performed by the DSC and the Lead Node will use SAS® Version 9.4 software. The Lead Node may also generate graphics using R Version 4.3.2.

14.0 UPDATES TO THE STATISTICAL ANALYSIS PLAN

Table 3. SAP revision history

SAP Version	Date of Approval	Summary of Changes
1.0		Initial Version

15.0 REFERENCES

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16.0 LIST OF PROPOSED TABLES, LISTINGS, AND FIGURES

The below table contains the tables, listings, and figures which will be provided by the DSC.

Section	Title	Population
Enrollment, Participant Disposition, and Visit Attendance	Summary of Screening by Site	Preliminary Screened
	Summary of Screens and Randomizations	Preliminary Screened
	Randomizations by Site, Strata and Treatment Arm	ITT
	Proposed and Actual Randomizations by Site	ITT
	Figure of Proposed and Actual Randomizations Overall	ITT
	Figure of Proposed and Actual Randomizations by Site	ITT
	Summary of Participant Disposition by Site	ITT
	Summary of Participant Disposition by Treatment Arm	ITT
	CONSORT Diagram	ITT
	Summary of Attendance at Treatment Period Visits by Site	ITT
	Summary of Attendance at Treatment Period Visits by Treatment Arm	ITT
	Summary of Attendance at Follow-up Visits by Site	ITT
	Summary of Attendance at Follow-up Visits by Treatment Arm	ITT
	Summary of Missed Visits During Treatment Period by Site	ITT
	Summary of Missed Visits During Treatment Period by Treatment Arm	ITT
	Summary of Missed Visits During Follow-up Period by Site	ITT
	Summary of Missed Visits During Follow-up Period by Treatment Arm	ITT
Participant Baseline Characteristics	Summary of Baseline Characteristics by Site	ITT
	Summary of Baseline Characteristics by Treatment Arm	ITT
	Summary of Baseline Characteristics in Study Completers by Treatment Arm	Study Completers
Treatment Exposure	Summary of Early Treatment Terminations in PILOT Intervention by Site	ITT
	Summary of Treatment Exposure in PILOT Intervention: Contacts by Site and Engagement Category	ITT
	Summary of Treatment Exposure in PILOT Intervention: Time Spent Engaging in Intervention by Site and Intervention Period	ITT
Primary Outcome	Summary of Primary Outcome Availability by Site	ITT

Section	Title	Population
	Summary of Primary Outcome Availability by Treatment Arm	ITT
	Summary of Primary Outcome Analysis by Treatment Arm	ITT
Supportive Analyses to the Primary Outcomes	Summary of Primary Outcome by Sex and Treatment Arm	ITT
	Summary of Primary Outcome by Age and Treatment Arm	ITT
	Summary of Primary Outcome by Race and Treatment Arm	ITT
	Summary of Primary Outcome by Ethnicity and Treatment Arm	ITT
	Summary of Primary Outcome by Homelessness Status and Treatment Arm	ITT
	Summary of Primary Outcome Sensitivity Analysis by Treatment Arm	ITT
Secondary Outcomes	Summary of Risk Behaviors Analysis at Day 30 by Treatment Arm	ITT
	Summary of Risk Behaviors Analysis at Day 90 by Treatment Arm	ITT
	Summary of Steps Achieved Along a Modified SUD Cascade of Care Availability by Site	ITT
	Summary of Steps Achieved Along a Modified SUD Cascade of Care Availability by Treatment Arm	ITT
	Summary of Secondary Outcome Analysis: Steps Achieved Along a Modified SUD Cascade of Care by Treatment Arm	ITT
	Summary of Steps Achieved Along a Modified SUD Cascade of Care by Treatment Arm	ITT
	Summary of Potentially Eligible Patients Willing to be Engaged over Number of Patients Approached	Approached
	Summary of Length of Engagement and Enrollment in PILOT	ITT
Supportive Analyses to the Secondary Outcome	Summary of Secondary Outcome Analysis: Steps Achieved Along a Modified SUD Cascade of Care by Primary Substance Use Disorder and Treatment Arm	ITT
Safety Outcomes	Summary of Hospitalizations by Treatment Arm	Safety
	Listing of Hospitalizations by Treatment Arm	Safety
	Summary of ED Visits by Treatment Arm	Safety
	Listing of ED Visits by Treatment Arm	Safety
	Summary of Non-fatal Overdoses by Treatment Arm	Safety

Section	Title	Population
	Listing of Non-fatal Overdoses by Treatment Arm	Safety
	Summary of Suicide Risk by Treatment Arm	Safety
	Listing of Suicide Risk by Treatment Arm	Safety
	Listing of Deaths by Treatment Arm	Safety
Data Quality	Summary of Data Audits	N/A
Protocol Deviations	Summary of Protocol Deviations by Site	N/A
	Listing of Protocol Deviations	N/A
Safety Narratives	Death Narratives	Safety

17.0 APPENDICES

17.1 Table of Contents

Tables

Figures

Listings

17.1.1 Enrollment, Participant Disposition, and Visit Attendance

Table 1: Summary of Screening by Site				
	Site 1	**Site 2**	**Site 3**	**Total**
Number of verbal consents	N			
Number of ineligible preliminary screens	N (X.x%)			
Criteria resulting in ineligibility at preliminary screening[1]				
Less than 18 years old	N (X.x%)			
Does not meet preliminary screening criteria for non-fatal overdose involving opioids				
Intentional opioid related overdose				
Participant does not have two contacts				
Participant does not agree to providing release of information				
Currently in jail, prison, or police custody				
Presented to ED more than 48 hours ago				
Unable to confirm future SUD treatment				
Unable to complete study baseline procedures due to medical or psychiatric condition				
Previously randomized as a participant in the study				
Unable to attend follow-up sessions				
Other				
Number of eligible preliminary screens not assessed in screening [2]	N (X.x%)			
Number screened	N			
Number of ineligible screens[3]	N (X.x%)			
Criteria resulting in ineligibility at screening[1]				
Inclusion criteria				
18 years old or older	N (X.x%)			
Meets screening criteria for non-fatal overdose involving opioids (NFOO)				
If community recruited: Self-reported a known or suspected overdose involving opioids in the past 30 days that involved transport or admission to an ED				
Able to provide sufficient locator information				
Willing and able to confirm future SUD treatment receipt				
Able to speak English sufficiently to understand study procedures and provide written informed consent				
Exclusion criteria				
Identified as having an intentional overdose as the Index NFOO	N (X.x%)			
Actively suicidal at the time of screening				

Table 1: Summary of Screening by Site				
	Site 1	**Site 2**	**Site 3**	**Total**
Unable to complete study baseline procedures due to medical or psychiatric condition				
Previously randomized as a participant in the study				
Unwilling or unable to follow study procedures				
Currently in jail, prison, or police custody				
Other reasons for screen failure[1]				
Unable to contact	N (X.x%)			
Reason 2				
Reason 3				
Number of participants eligible but not randomized[4]	N (X.x%)			
Reason not randomized[5]				
Declined study participation	N (X.x%)			
Death				
Left study prior to randomization				
Other				
Number of participants ineligible but randomized[6]				

[1] Percentages are calculated based on the denominator of the number that screened ineligible during preliminary screening or that screened ineligible during screening assessment and may sum to greater than 100% if multiple eligibility criteria are not met for potential participants.

[2] Percentages are calculated based on the denominator of the number that screened eligible during preliminary screening.

[3] Percentages are calculated based on the denominator of the number that screened.

[4] Percentages are calculated based on the denominator of the number that screened eligible during screening assessment.

[5] Percentages are calculated based on the denominator of the number of participants eligible but not randomized.

[6] Percentages are calculated based on the denominator of the number of participants randomized.

Table 2: Summary of Screens and Randomizations									
Site	**Number of Preliminary Screens**	**Number of Screens**	**Percent of Eligible Preliminary Screens Screened**	**Number of Ineligible Screens**	**Percent of Ineligible Screens**	**Number Eligible but Not Randomized**	**Number Randomized**	**Percent of Eligible Preliminary Screens Randomized**	**Percent of Screens Randomized**
Site 1	N	N	X.x%	N	X.x%	N	N	N	X.x%
Site 2									
Site 3									
Total									

Table 3: Randomizations by Site, Strata, and Treatment Arm				
	Strata	**Treatment Arm[1]**		
Site	**Homeless Status**	**TAU (N=XX)**	**PILOT (N=XX)**	**Total[2] (N=XX)**
Site 1	Homeless	N (X.x%)	N (X.x%)	N (X.x%)
	Not Homeless			
Site 2	Homeless			
	Not Homeless			
Site 3	Homeless			
	Not Homeless			
Total	Homeless			
	Not Homeless			
	Overall[3]			

[1] Percentage is calculated based on the denominator of number of participants in each treatment arm and at each site or overall.

[2] Percentage is calculated based on the denominator of the number of participants at each site or overall.

[3] Percentage is calculated based on the denominator of the number of participants randomized

Table 4: Proposed and Actual Randomizations by Site						
Site	**Proposed Randomization**	**Date Site Opened for Enrollment**	**Date of First Randomization**	**Actual Randomizations**	**Actual/ Proposed (%)**	**Date of Last Randomization**
Site 1	N	mm/dd/yyyy	mm/dd/yyyy	N	X.x%	mm/dd/yyyy
Site 2						
Site 3						
Total						

Figure 1: Expected and Actual Randomizations Overall

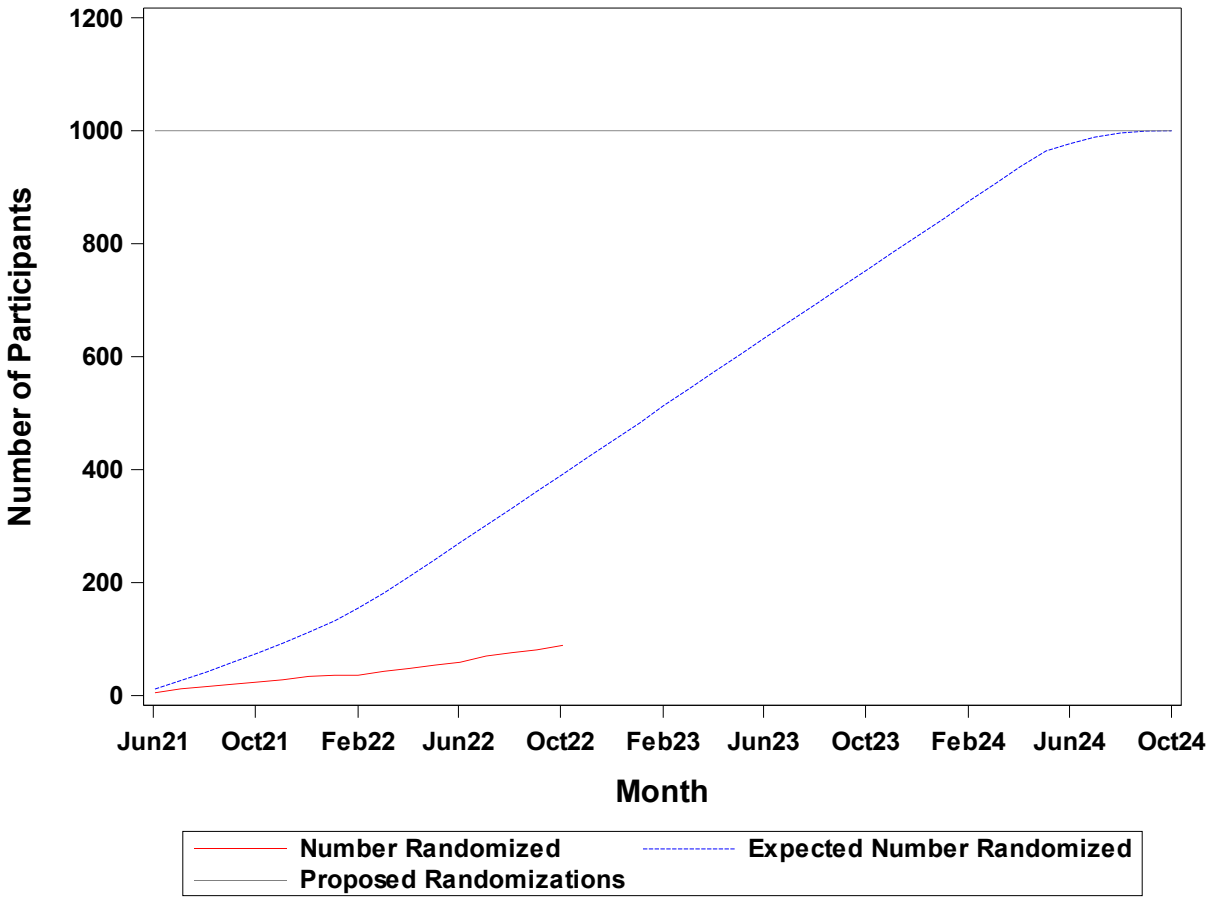

Figure 2: Expected and Actual Randomizations by Site

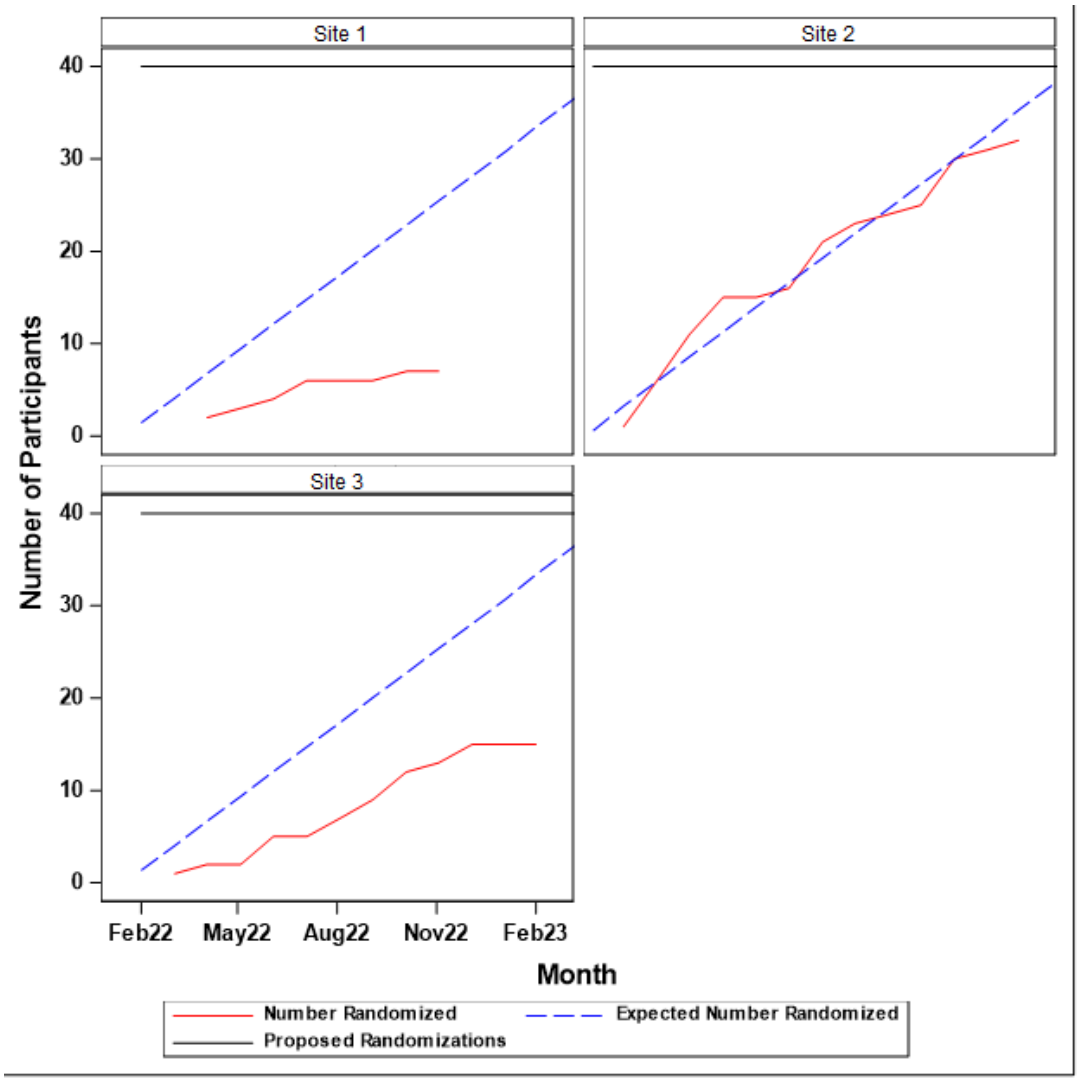

Table 5: Summary of Participant Disposition by Site				
	Site 1	**Site 2**	**Site 3**	**Total**
Number of participants randomized	N			
Number of study completers[1]	N (X.x%)			
Number of early study terminations[2]	N (X.x%)			
Reason for early study termination[3]				
Participant failed to return to clinic and unable to contact	N (X.x%)			
Participant stopped participation due to practical problems (e.g., no childcare or transportation)				
Participant moved from area				
Participant incarcerated				
Participant terminated due to AE/SAE				
Participant terminated for other clinical reasons				
Participant had a significant psychiatric risk (e.g., suicidal, homicidal, psychotic)				
Participant withdrew consent				
Participant deceased				
Participant terminated for administrative issues				
Participant terminated due to pressure or advice from outsiders				
Participant feels treatment no longer necessary, cured				
Participant feels treatment no longer necessary, not working				
COVID-19: Illness				
COVID-19: Public health measures				
COVID-19: Other				
Participant terminated for other reason				

[1] A participant is a study completer if they had a Study Completion (STC) form indicating completion of the study.

[2] A participant is an early study termination if they had a STC form indicating they did not complete the study.

[3] Percentage is calculated based on the denominator of number of early terminations.

Table 6: Summary of Participant Disposition by Treatment Arm			
	Treatment Arm		
	TAU	PILOT	Total
Number of participants randomized	N		
Number of study completers[1]	N (X.x%)		
Number of early study terminations[2]	N (X.x%)		
Reason for early study termination[3]			
Participant failed to return to clinic and unable to contact	N (X.x%)		
Participant stopped participation due to practical problems (e.g., no childcare or transportation)			
Participant moved from area			
Participant incarcerated			
Participant terminated due to AE/SAE			
Participant terminated for other clinical reasons			
Participant had a significant psychiatric risk (e.g., suicidal, homicidal, psychotic)			
Participant withdrew consent			
Participant deceased			
Participant terminated for administrative issues			
Participant terminated due to pressure or advice from outsiders			
Participant feels treatment no longer necessary, cured			
Participant feels treatment no longer necessary, not working			
COVID-19: Illness			
COVID-19: Public health measures			
COVID-19: Other			
Participant terminated for other reason			

[1] A participant is a study completer if they had a Study Completion (STC) form indicating completion of the study.
[2] A participant is an early study termination if they had a STC form indicating they did not complete the study.
[3] Percentage is calculated based on the denominator of number of early terminations.

Figure 3:Consort Diagram

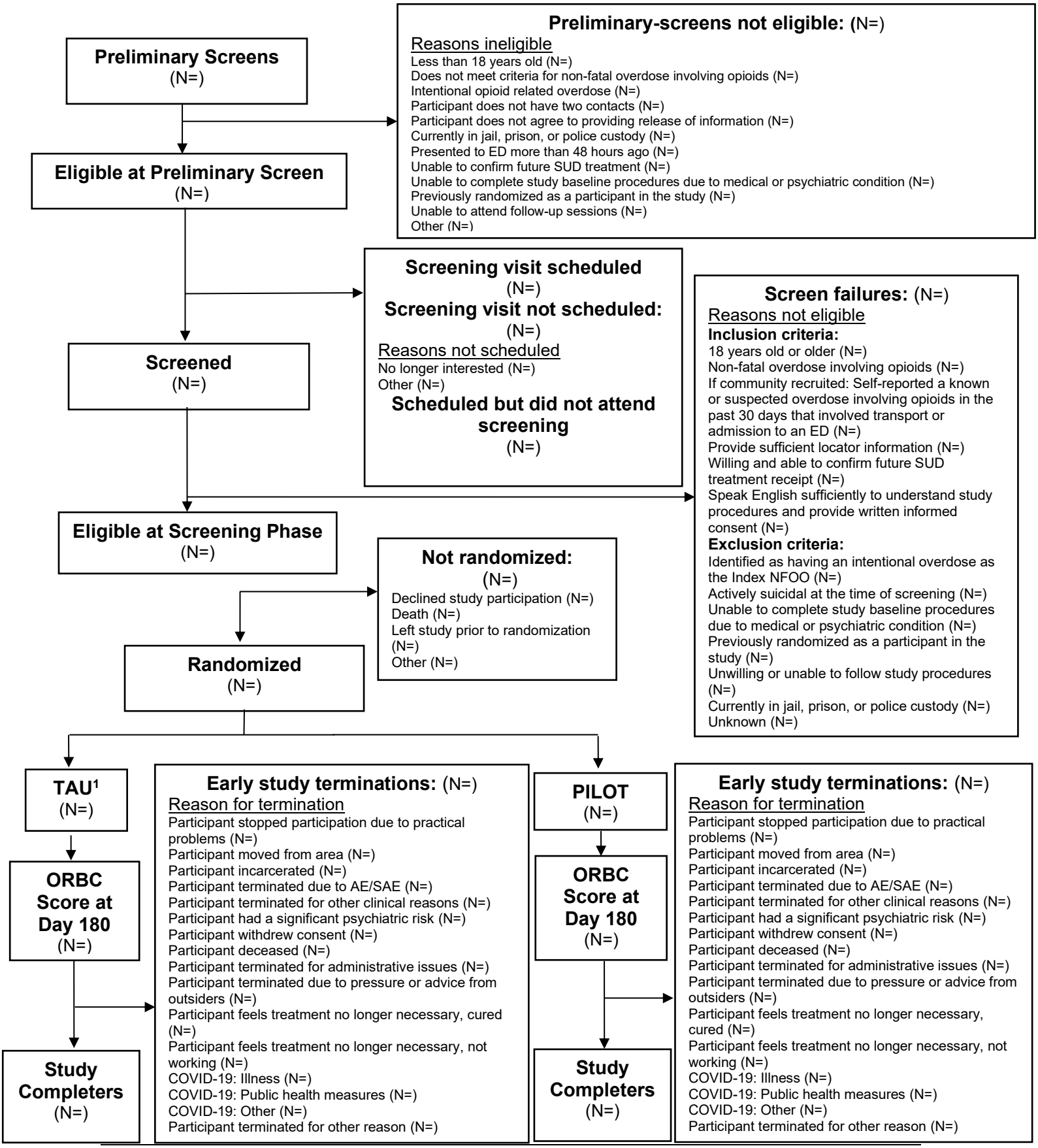

Table 7: Summary of Attendance at Treatment Period Visits by Site					
Site	**Number of Participants Randomized**	**Participants who Attended Day 30 Visit[1]**	**Participants who Attended Day 90 Visit[1]**	**Participants who Attended Day 180 Visit[1]**	**Percentage of Visits Attended[1,2]**
Site 1	N	N (X.x%)	N (X.x%)	N (X.x%)	N (X.x%)
Site 2					
Site 3					
Total					

[1] Percentage is calculated as number of participants who attended the visit divided by number of participants randomized. Visit was considered attended if the Visit Documentation form (V07) indicated that the visited was attended.

[2] Percentage is calculated as the number of visits attended divided by the number of visits (number of participants randomized times the number of visits).

Table 8: Summary of Attendance at Treatment Period Visits by Treatment Arm					
Treatment Arm	**Number of Participants Randomized**	**Participants who Attended Day 30 Visit[1]**	**Participants who Attended Day 90 Visit[1]**	**Participants who Attended Day 180 Visit[1]**	**Percentage of Visits Attended[1,2]**
TAU	N	N (X.x%)	N (X.x%)	N (X.x%)	N (X.x%)
PILOT					
Total					

[1] Percentage is calculated as number of participants who attended the visit divided by number of participants randomized. Visit was considered attended if the Visit Documentation form (V07) indicated that the visited was attended.

[2] Percentage is calculated as the number of visits attended divided by the number of study visits (number of participants randomized times the number of visits).

Table 9: Summary of Attendance at Follow-up Visits by Site			
Site	Number of Participants Randomized	Day 210 Follow-up Visit	
		Number Attended[1]	Percentage Attended
Site 1	N	N	X.x%
Site 2			
Site 3			
Total			

[1] Visit is considered attended if the Visit Documentation form (V07) indicated that the visited was attended.

Table 10: Summary of Attendance at Follow-up Visits by Treatment Arm			
Treatment Arm	Number of Participants Randomized	Day 210 Follow-up Visit	
		Number Attended[1]	Percentage Attended
TAU	N	N	X.x%
PILOT			
Total			

[1] Visit is considered attended if the Visit Documentation form (V07) indicates that the visited was attended.

Table 11: Summary of Missed Visits During Treatment Period by Site				
	Site 1 (N=XX)	**Site 2 (N=XX)**	**Site 3 (N=XX)**	**Total (N=XX)**
Number of expected visits[1]	N			
Number of missed visits due to early study termination[2]	N (X.x%)			
Number of missed visits during active participation[2,3]				
Number of participants with at least one missed visit[4]	N (X.x%)			
Average number of missed visits per participant[5]	X.X			
Reason for missed visit during active participation[6]				
Participant on vacation	N (X.x%)			
Participant illness				
Participant in hospital, inpatient, or residential treatment				
Participant moved from area				
Participant incarcerated				
Site closed				
Participant withdrew consent				
Participant deceased				
Participant unable to attend visit due to logistical barriers				
Visit was not scheduled				
Unable to contact				
Site decision/error				
COVID-19: Illness				
COVID-19: Public health measures				
COVID-19: Other				
Other				
Reason missing				

[1] Expected visits include visits at Day 30, Day 90, and Day 180. Visits are considered expected starting on the day after the window closes.

[2] Percentage is calculated based on the denominator of number of expected visits.

[3] Includes participants who missed visit prior to the STC form being completed indicating early study termination.

[4] Percentage is calculated based on the denominator of number of participants randomized.

[5] Average number of missed visits per participant with at least one missed visit.

[6] Percentages are calculated based on the denominator of number of missed visits during active participation.

Table 12: Summary of Missed Visits During Treatment Period by Treatment Arm			
	Treatment Arm		
	TAU (N=XX)	PILOT (N=XX)	Total (N=XX)
Number of expected visits[1]	N		
Number of missed visits due to early study terminations[2]	N (X.x%)		
Number of missed visits during active participation[2,3]			
Number of participants with at least one missed visit[4]	N (X.x%)		
Average number of missed visits per participant[5]	X.X		
Reason for missed visit during active participation[6]			
Participant on vacation	N (X.x%)		
Participant illness			
Participant in hospital, in-patient, or residential treatment			
Participant moved from area			
Participant incarcerated			
Site closed			
Participant withdrew consent			
Participant deceased			
Participant unable to attend visit due to logistical barriers			
Visit was not scheduled			
Unable to contact			
Site decision/error			
COVID-19: Illness			
COVID-19: Public health measures			
COVID-19: Other			
Other			
Reason missing			

[1] Expected visits include visits at Day 30, Day 90, and Day 180. Visits are considered expected starting on the day after the window closes.

[2] Percentage is calculated based on the denominator of number of expected visits.

[3] Includes participants who missed visits prior to the STC form being completed indicating early study termination.

[4] Percentage is calculated based on the denominator of number of participants randomized.

[5] Average number of missed visits per participant with at least one missed visit.

[6] Percentages are calculated based on the denominator of number of missed visits during active participation.

Table 13: Summary of Missed Visits During Follow-up Period by Site				
	Site 1 (N=XX)	**Site 2 (N=XX)**	**Site 3 (N=XX)**	**Total (N=XX)**
Number of expected visits[1]	N			
Number of missed visits due to early study terminations[2]	N (X.x%)			
Number of missed visits during active participation[2,3]				
Number of participants with at least one missed visit[4]	N (X.x%)			
Average number of missed visits per participant[5]	X.X			
Reason for missed visit during active participation[6]				
Participant on vacation	N (X.x%)			
Participant illness				
Participant in hospital, inpatient, or residential treatment				
Participant moved from area				
Participant incarcerated				
Site closed				
Participant withdrew consent				
Participant deceased				
Participant unable to attend visit due to logistical barriers				
Visit was not scheduled				
Unable to contact				
Site decision/error				
COVID-19: Illness				
COVID-19: Public health measures				
COVID-19: Other				
Other				
Unknown				

[1] Expected visits include visits at Day 210. Visits are considered expected starting on the day after the window closes.

[2] Percentage is calculated based on the denominator of number of expected visits.

[3] Includes participants who missed visits prior to the STC form being completed indicating early study termination.

[4] Percentage is calculated based on the denominator of number of participants randomized.

[5] Average number of missed visits per participant with at least one missed visit.

[6] Percentages are calculated based on the denominator of number of missed visits during active participation.

Table 14: Summary of Missed Visits During Follow-up Period by Treatment Arm			
	Treatment Arm		
	TAU (N=XX)	PILOT (N=XX)	Total (N=XX)
Number of expected visits[1]	N		
Number of missed visits due to early study terminations[2]	N (X.x%)		
Number of missed visits during active participation[2,3]			
Number of participants with at least one missed visit[4]	N (X.x%)		
Average number of missed visits per participant[5]	X.X		
Reason for missed visit during active participation[6]			
Participant on vacation	N (X.x%)		
Participant illness			
Participant in hospital, in-patient, or residential treatment			
Participant moved from area			
Participant incarcerated			
Site closed			
Participant withdrew consent			
Participant deceased			
Participant unable to attend visit due to logistical barriers			
Participant failed to return to site and unable to contact			
Visit was not scheduled			
Unable to contact			
Site decision/error			
COVID-19: Illness			
COVID-19: Public health measures			
COVID-19: Other			
Other			
Unknown			

[1] Expected visits include visits at Day 210. Visits are considered expected starting on the day after the window closes.

[2] Percentage is calculated based on the denominator of number of expected visits.

[3] Includes participants who missed visits prior to the STC form being completed indicating early study termination.

[4] Percentage is calculated based on the denominator of number of participants randomized.

[5] Average number of missed visits per participant with at least one missed visit.

[6] Percentages are calculated based on the denominator of number of missed visits during active participation.

17.1.2 Participant Baseline Characteristics

Table 15: Summary of Baseline Characteristics by Site				
	Site 1 (N=XX)	**Site 2 (N=XX)**	**Site 3 (N=XX)**	**Total (N=XX)**
Sex (at birth)				
Missing	N (X.x%)			
Male				
Female				
Don't know				
Refused to answer				
Age in years (Mean (SD))	X.X (X.XX)			
Age in years				
Missing	N (X%)			
< 18				
18 - < 25				
25 - < 35				
35 - < 45				
45 - < 55				
55 - < 65				
65 - < 75				
75+				
Ethnicity				
Missing	N (X.x%)			
Not Hispanic or Latinx				
Hispanic or Latinx				
Don't know				
Refused to answer				
Race				
Missing	N (X.x%)			
American Indian or Alaska Native				
Asian				
Black or African American				
Native Hawaiian or Pacific Islander				
White				
Other				
Multiracial				
Don't know				
Refused to answer				

Table 15: Summary of Baseline Characteristics by Site				
	Site 1 (N=XX)	**Site 2 (N=XX)**	**Site 3 (N=XX)**	**Total (N=XX)**
Education completed				
Missing	N (X.x%)			
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				
Missing	N (X.x%)			
Married				
Widowed				
Divorced				
Separated				
Never married				
Living with partner				
Don't know				
Refused				
Employment				
Missing	N (X.x%)			
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 15: Summary of Baseline Characteristics by Site				
	Site 1 (N=XX)	**Site 2 (N=XX)**	**Site 3 (N=XX)**	**Total (N=XX)**
Housing Status				
Stable housing (living in stable housing that they own, rent, or stay in as part of a household)	N (X.x%)			
Unstable housing (staying with friends, not/unable to pay rent)				
Homeless (staying in shelter or streets)				
Substance Use Disorder (any severity)				
Opioids	N (X.x%)			
Alcohol				
Amphetamines				
Cannabis				
Cocaine				
Sedatives				
Opioid Use Disorder Severity				
None	N (X.x%)			
Mild				
Moderate				
Severe				
Number of SUD per participant				
N	X			
Mean	X.x			
SD	X.xx			
Min	X			
25th Percentile	X.x			
Median	X.x			
75th Percentile	X.x			
Max	X			
Number of lifetime overdoses				
N				
Mean				
SD				
Min				
25th Percentile				
Median				
75th Percentile				
Max				

Table 15: Summary of Baseline Characteristics by Site				
	Site 1 (N=XX)	**Site 2 (N=XX)**	**Site 3 (N=XX)**	**Total (N=XX)**
Time since last OD (days)				
N				
Mean				
SD				
Min				
25th Percentile				
Median				
75th Percentile				
Max				
ORBC score at baseline				
N				
Mean				
SD				
Min				
25th Percentile				
Median				
75th Percentile				
Max				

Table 16: Summary of Baseline Characteristics by Treatment Arm			
	Treatment Arm		
	TAU (N=XX)	PILOT (N=XX)	Total (N=XX)
Sex (at birth)			
Missing	N (X.x%)		
Male			
Female			
Don't know			
Refused to answer			
Age in years (Mean (SD))	X.X (X.XX)		
Age in years			
Missing	N (X.x%)		
< 18			
18 - < 25			
25 - < 35			
35 - < 45			
45 - < 55			
55 - < 65			
65 - < 75			
75+			
Ethnicity			
Missing	N (X.x%)		
Not Hispanic or Latinx			
Hispanic or Latinx			
Don't know			
Refused to answer			
Race			
Missing	N (X.x%)		
American Indian or Alaska Native			
Asian			
Black or African American			
Native Hawaiian or Pacific Islander			
White			
Other			
Multiracial			

Table 16: Summary of Baseline Characteristics by Treatment Arm			
	Treatment Arm		
	TAU (N=XX)	PILOT (N=XX)	Total (N=XX)
Don't know			
Refused to answer			
Education completed			
Missing	N (X.x%)		
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			
Missing	N (X.x%)		
Married			
Widowed			
Divorced			
Separated			
Never married			
Living with partner			
Don't know			
Refused			
Employment			
Missing	N (X.x%)		
Working now			
Only temporarily laid off, sick leave, or maternity leave			
Looking for work, unemployed			
Retired			

Table 16: Summary of Baseline Characteristics by Treatment Arm			
	Treatment Arm		
	TAU (N=XX)	PILOT (N=XX)	Total (N=XX)
Disabled permanently or temporarily			
Keeping house			
Student			
Other			
Housing Status			
Stable housing (living in stable housing that they own, rent, or stay in as part of a household)			
Unstable housing (staying with friends, not/unable to pay rent)			
Homeless (staying in shelter or streets)			
Substance Use Disorder (any severity)			
Opioids			
Alcohol			
Amphetamines			
Cannabis			
Cocaine			
Sedatives			
Opioid Use Disorder Severity			
None			
Mild			
Moderate			
Severe			
Number of SUD per participant			
N			
Mean			
SD			
Min			
25th Percentile			
Median			
75th Percentile			
Max			
Number of lifetime overdoses			
N			

Table 16: Summary of Baseline Characteristics by Treatment Arm			
	Treatment Arm		
	TAU (N=XX)	PILOT (N=XX)	Total (N=XX)
Mean			
SD			
Min			
25th Percentile			
Median			
75th Percentile			
Max			
Time since last OD (days)			
N			
Mean			
SD			
Min			
25th Percentile			
Median			
75th Percentile			
Max			
ORBC score at baseline			
N			
Mean			
SD			
Min			
25th Percentile			
Median			
75th Percentile			
Max			

Table 17: Summary of Baseline Characteristics in Study Completers by Treatment Arm			
	Treatment Arm		
	TAU (N=XX)	PILOT (N=XX)	Total (N=XX)
Sex (at birth)			
Missing	N (X.x%)		
Male			
Female			
Don't know			
Refused to answer			
Age in years (Mean (SD))	X.X (X.XX)		
Age in years			
Missing	N (X.x%)		
< 18			
18 - < 25			
25 - < 35			
35 - < 45			
45 - < 55			
55 - < 65			
65 - < 75			
75+			
Ethnicity			
Missing	N (X.x%)		
Not Hispanic or Latinx			
Hispanic or Latinx			
Don't know			
Refused to answer			
Race			
Missing	N (X.x%)		
American Indian or Alaska Native			
Asian			
Black or African American			
Native Hawaiian or Pacific Islander			
White			
Other			

Table 17: Summary of Baseline Characteristics in Study Completers by Treatment Arm			
	Treatment Arm		
	TAU (N=XX)	PILOT (N=XX)	Total (N=XX)
Multiracial			
Don't know			
Refused to answer			
Education completed			
Missing	N (X.x%)		
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			
Missing	N (X.x%)		
Married			
Widowed			
Divorced			
Separated			
Never married			
Living with partner			
Don't know			
Refused			
Employment			
Missing	N (X.x%)		
Working now			
Only temporarily laid off, sick leave, or maternity leave			

Table 17: Summary of Baseline Characteristics in Study Completers by Treatment Arm			
	Treatment Arm		
	TAU (N=XX)	PILOT (N=XX)	Total (N=XX)
Looking for work, unemployed			
Retired			
Disabled permanently or temporarily			
Keeping house			
Student			
Other			
Housing Status			
Stable housing (living in stable housing that they own, rent, or stay in as part of a household)			
Unstable housing (staying with friends, not/unable to pay rent)			
Homeless (staying in shelter or streets)			
Substance Use Disorder (any severity)			
Opioids	N (X.x%)		
Alcohol			
Amphetamines			
Cannabis			
Cocaine			
Sedatives			
Opioid Use Disorder Severity			
None	N (X.x%)		
Mild			
Moderate			
Severe			
Number of SUD per participant			
N	X		
Mean	X.x		
SD	X.xx		
Min	X		
25th Percentile	X.x		
Median	X.x		
75th Percentile	X.x		
Max	X		

Table 17: Summary of Baseline Characteristics in Study Completers by Treatment Arm			
	Treatment Arm		
	TAU (N=XX)	PILOT (N=XX)	Total (N=XX)
Number of lifetime overdoses			
N			
Mean			
SD			
Min			
25th Percentile			
Median			
75th Percentile			
Max			
Time since last OD (days)			
N			
Mean			
SD			
Min			
25th Percentile			
Median			
75th Percentile			
Max			
ORBC score at baseline			
N			
Mean			
SD			
Min			
25th Percentile			
Median			
75th Percentile			
Max			

17.1.3 Treatment Exposure

Table 18: Summary of Early Treatment Terminations in PILOT Intervention by Site				
	Site 1 (N=XX)	**Site 2 (N=XX)**	**Site 3 (N=XX)**	**Total (N=XX)**
Number of early study treatment terminations prior to Month 6[1]	N (X.x%)			
Reason for early treatment termination[2]				
Participant refused, non-specific	N (X.x%)			
Participant left study and never returned				
Clinical deterioration: new onset of psychiatric or medical condition				
Physical illness or condition that precludes study intervention				
Participant feels study intervention no longer necessary, cured				
Participant feels study intervention no longer necessary, not working				
Participant relayed unwanted side effects, inconvenience or discomfort from study intervention				
Participant moved from area				
Time commitment				
COVID-19: Illness				
COVID-19: Public health measures				
COVID-19: Other				
Participant deceased				
Participant withdrew consent				
Other				

[1] Percentage is out of the total number of participants randomized to the PILOT intervention.

[2] Percentages are out of the total number of early treatment terminations.

Table 19: Summary of Treatment Exposure in PILOT Intervention: Contacts by Site and Engagement Category						
Site		**Engagement Category[1]**				**Overall Engaged[2]**
		Missing	**Unengaged**	**Partially Engaged**	**Engaged**	
Site 1	Number of contacts attempted[3]	N				
	Number of contacts attempted per participant per week					
	Mean	XX				
	SD	xx.x				
	Min	XX				
	25th Percentile	XX				
	Median	XX				
	75th Percentile	XX				
	Max	XX				
	Number of contacts completed[3]					
	Number of contacts completed per participant per week					
	Mean					
	SD					
	Min					
	25th Percentile					
	Median					
	75th Percentile					
	Max					
Site 2						
Site 3						
Total						

[1] Engagement category was assessed on the first day of the 7-day period on the Peer Intervention Log (PIL).

[2] Overall engaged includes partially engaged and engaged.

[3] Contacts attempted and completed was captured daily on the PIL.

Table 20: Summary of Treatment Exposure in PILOT Intervention: Time Spent Engaging in Intervention Activities by Site and Intervention Period

Site	Study Period	Time Spent Engaging in Intervention Activities[1]							
		Missing	No time spent (0 minutes)	1 - <15 minutes	15-30 minutes	31-45 minutes	46-60 minutes	> 1 hour	Overall 1+ minutes
Site1	Day 1 – 30	N (X.x%)	N (X.x%)	N (X.x%)	N (X.x%)	N (X.x%)	N (X.x%)	N (X.x%)	N (X.x%)
	Day 31 – 60	…							
	Day 61 – 90	…							
	Day 91 – 120								
	Day 121 – 150								
	Day 151 – 180								
	Day 181 – 210[2]								
	Total	…							
Site 2	…								
Site 3	…								
Total	…								

[1] Time spent engaging in intervention activities was captured daily on the Peer Intervention Log (PIL).

[2] PIL entries through the end of the follow-up visit window (Study Day 225) are included in the final intervention study period.

17.1.4 Primary Outcome

Table 21: Summary of Primary Outcome Availability by Site

Site	Number of Participants Randomized	Number of Participants with ORBC[1] Score Collected			
		Baseline	Day 30	Day 90	Day 180
Site 1	N	N (X.x%)	N (X.x%)	N (X.x%)	N (X.x%)
Site 2					
Site 3					
Total					

[1] Overdose Risk Behavior Checklist (ORBC; ORB form) captured the frequency of self-reported overdose risk behaviors at Day 30, Day 90, and Day 180. The primary outcome is collected at Day 180. Percentage is calculated as number collected divided by number of randomized participants.

Table 22: Summary of Primary Outcome Availability by Treatment Arm					
Treatment Arm	**Number of Participants Randomized**	**Number of Participants with ORBC[1] Score Collected**			
		Baseline	**Day 30**	**Day 90**	**Day 180**
TAU	N	N (X.x%)	N (X.x%)	N (X.x%)	N (X.x%)
PILOT					
Total					

[1] Overdose Risk Behavior Checklist (ORBC; ORB form) captured the frequency of self-reported overdose risk behaviors at Day 30, Day 90, and Day 180. The primary outcome is collected at Day 180. Percentage is calculated as number collected divided by number of randomized participants.

Table 23: Summary of Primary Outcome Analysis by Treatment Arm

Treatment Arm	Number of Participants Randomized	Number of Participants Contributing to Day 180 Estimate[1]	Unadjusted ORBC Score Collected at Day 180[2] (Mean (SD))	Results[3]			
				Rate Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
TAU	N	N (%)	X .x (X.xx)	X.xx	X.xx	X.xx	0.xxx
PILOT							
Total							

[1] A participant contributes to the Day 180 estimate if they have all fixed effect covariates and an ORBC score at Day 180.

[2] Unadjusted ORBC scores are reported for participants who contribute to the Day 180 estimate.

[3] Results are obtained from the longitudinal mixed effects model. The rate ratio and p-value result from the interaction term between treatment arm and day at Day 180. Missing ORBC scores are not imputed.

17.1.5 Supportive Analyses of the Primary Outcome Measure

Table 24: Summary of Primary Outcome by Sex and Treatment Arm

Subgroup	Number of Participants Randomized	Treatment Arm: TAU (N =XX) ORBC Score Collected at Day 180 (Mean (SD))	Treatment Arm: PILOT (N =XX) ORBC Score Collected at Day 180 (Mean (SD))	Results[1] Rate Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
Male	N	X.X (X.XX)	X.X (X.XX)	X.XX	X.XX	X.XX	0.xxx
Female							

[1] Results are obtained from the longitudinal mixed effects model. The p-value for the interaction term between treatment arm and subgroup is shown. Missing ORBC scores are not imputed.

Table 25: Summary of Primary Outcome by Age and Treatment Arm							
		Treatment Arm		Results[1]			
		TAU (N =XX)	PILOT (N =XX)				
Subgroup	Number of Participants Randomized	ORBC Score Collected at Day 180 (Mean (SD))	ORBC Score Collected at Day 180 (Mean (SD))	Rate Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
≤ 35 years	N	X.X (X.XX)	X.X (X.XX)	X.XX	X.XX	X.XX	0.xxx
> 35 years							

[1] Results are obtained from the longitudinal mixed effects model. The p-value for the interaction term between treatment arm and subgroup is shown. Missing ORBC scores are not imputed.

Table 26: Summary of Primary Outcome by Race and Treatment Arm							
		Treatment Arm		Results[1]			
		TAU (N =XX)	PILOT (N =XX)				
Subgroup	Number of Participants Randomized	ORBC Score Collected at Day 180 (Mean (SD))	ORBC Score Collected at Day 180 (Mean (SD))	Rate Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
Black	N	X.X (X.XX)	X.X (X.XX)	X.XX	X.XX	X.XX	0.xxx
White							
Other[2]							

[1] Results are obtained from the longitudinal mixed effects model. The p-value for the interaction term between treatment arm and subgroup is shown. Missing ORBC scores are not imputed.

[2] Other includes American Indian or Alaska Native, Asian, Native Hawaiian or Pacific Islander, Other and Multiracial.

Table 27: Summary of Primary Outcome by Ethnicity and Treatment Arm							
		Treatment Arm		Results[1]			
		TAU (N =XX)	PILOT (N =XX)				
Subgroup	Number of Participants Randomized	ORBC Score Collected at Day 180 (Mean (SD))	ORBC Score Collected at Day 180 (Mean (SD))	Rate Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
Not Hispanic or Latinx	N	X.X (X.XX)	X.X (X.XX)	X.XX	X.XX	X.XX	0.xxx
Hispanic or Latinx							

[1] Results are obtained from the longitudinal mixed effects model. The p-value for the interaction term between treatment arm and subgroup is shown. Missing ORBC scores are not imputed.

Table 28: Summary of Primary Outcome by Homelessness Status and Treatment Arm							
		Treatment Arm		Results[1]			
		TAU (N =XX)	PILOT (N =XX)				
Subgroup	Number of Participants Randomized	ORBC Score Collected at Day 180 (Mean (SD))	ORBC Score Collected at Day 180 (Mean (SD))	Rate Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
Homeless	N	X.X (X.XX)	X.X (X.XX)	X.XX	X.XX	X.XX	0.xxx
Not Homeless							

[1] Results are obtained from the longitudinal mixed effects model. The p-value for the interaction term between treatment arm and subgroup is shown. Missing ORBC scores are not imputed.

Table 29: Summary of Primary Outcome Sensitivity Analysis by Treatment Arm						
Method	**Results**	**N**	**Rate Ratio**	**95% Lower Confidence Limit**	**95% Upper Confidence Limit**	**p-value**
Protocol defined primary outcome	Secondary outcome (missing UDS not imputed)	N	X.XX	X.XX	X.XX	0.xxx
Strict study visit windows	ORBC scores collected outside the study visit window considered missing					
Imputation of missing ORBC Scores	Multiple imputation					

Table 30: Summary of Risk Behaviors Analysis at Day 30 by Treatment Arm							
			Results[3]				
Treatment Arm	Number of Participants Randomized	Number of Participants Contributing to Day 30 Estimate[1]	Unadjusted ORBC Score Collected at Day 30[2] Mean (SD)	Rate Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
TAU	N	N (%)	XX.x (X.x)	X.xx	X.xx	X.xx	0.xxx
PILOT							
Total							

[1] A participant contributes to the Day 30 estimate fi they have all fixed effect covariates and an ORBC score at Day 30.

[2] Unadjusted ORBC scores are reported for participants who contributed to the Day 30 estimate.

[3] Results are obtained from the longitudinal mixed effects model. The rate ratio and p-value result from the interaction term between treatment arm and day at Day 30. Missing ORBC scores are not imputed.

Table 31: Summary of Risk Behaviors Analysis at Day 90 by Treatment Arm							
			Results[3]				
Treatment Arm	Number of Participants Randomized	Number of Participants Contributing to Day 90 Estimate[1]	Unadjusted ORBC Score Collected at Day 90[2] Mean (SD)	Rate Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
TAU	N	N (%)	XX.x (X.x)	X.xx	X.xx	X.xx	0.xxx
PILOT							
Total							

[1] A participant contributes to the Day 90 estimate fi they have all fixed effect covariates and an ORBC score at Day 90.

[2] Unadjusted ORBC scores are reported for participants who contributed to the Day 90 estimate.

[3] Results are obtained from the longitudinal mixed effects model. The rate ratio and p-value result from the interaction term between treatment arm and day at Day 90. Missing ORBC scores are not imputed.

17.1.6 Secondary Outcomes

Table 32: Summary of Steps Achieved Along a Modified SUD Cascade of Care Availability by Site

		Number of Participants with Steps Achieved Available[1]		
Site	**Number of Participants Randomized**	**Day 30**	**Day 90**	**Day 180**
Site 1	N	N (X.x%)	N (X.x%)	N (X.x%)
Site 2				
Site 3				
Total				

[1] Availability is calculated as the number of expected forms (HRC, SAA, MCA, DSM, UDT, and ARC) collected per participant. The percentage is calculated as the number of available forms over the number of expected forms (6 forms x number of participants randomized).

Table 33: Summary of Steps Achieved Along a Modified SUD Cascade of Care Availability by Treatment Arm

		Number of Participants with Steps Achieved Available[1]		
Treatment Arm	**Number of Participants Randomized**	**Day 30**	**Day 90**	**Day 180**
TAU	N	N (X.x%)	N (X.x%)	N (X.x%)
PILOT				
Total				

[1] Availability is calculated as the number of expected forms (HRC, SAA, MCA, DSM, UDT, and ARC) collected per participant. The percentage is calculated as the number of available forms over the number of expected forms (6 forms times the number of participants randomized).

Table 34: Summary of Secondary Outcome Analysis: Steps Achieved Along a Modified SUD Cascade of Care by Treatment Arm

Treatment Arm	Number of Participants Randomized	Results[2]				
		Steps Achieved at Day 180[1] Mean (SD)	Rate Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
TAU	N	X (X.x)	X.xx	X.xx	X.xx	0.xxx
PILOT						
Total						

[1] Steps achieved is collected on the following forms: HRC, SAA, MCA, DSM, UDT, and ARC

[2] Results are obtained from the longitudinal mixed effects model. The rate ratio and p-value result from the interaction term between treatment arm and day at Day 180.

Table 35*:* Summary of Steps Achieved Along a Modified SUD Cascade of Care by Treatment Arm

Total Number of Steps Achieved at Day 180	Treatment Arm		Total (N=XX)
	TAU (N=XX)	PILOT (N=XX)	
0	N (X.x%)		
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
Steps Achieved at Day 180			
N	X		
Mean	X.x		
SD	X.xx		
Min	X		
25th Percentile	X.x		
Median	X.x		
75th Percentile	X.x		
Max	X		
Number of Participants who completed each step			
1. Increase in harm reduction exposure and behaviors	N (%)		
2. Engagement in Care - Any			
3. Engagement in Care - Regular			
4. Taking MOUD – Any			
5. Taking MOUD consistently over the past 30 days			
6. Taking MOUD consistently over the past 90 days			
7. Taking MOUD consistently for 180 days			
8. Decrease SUD severity			
9. Early remission			
10. Increase in recovery capital score			

Table 36: Summary of Potentially Eligible Patients Willing to be Engaged over Number of Approached

Number of Potentially Eligible Patients Approached[1]	Number of Participants Willing to be Enrolled[2]	Results[3]		
		Proportion	95% Lower Confidence Limit	95% Upper Confidence Limit
N	N	X.x%	X.xx	X.xx

[1] The number of participants approached is captured on the Screening Approach (SCA) form.

[2] Willingness to be enrolled is defined as providing verbal consent and is captured on the ENRA or ENRY enrollment form.

[3] Results are obtained from the Wald confidence limits.

Table 37: Summary of Length of Engagement and Enrollment in PILOT								
Number of Participants Enrolled in PILOT	**Average Length of Engagement[1]**					**Results[2]**		
	Minimum	**25th Percentile**	**Median**	**75th Percentile**	**Maximum**	**Mean (SD)**	**95% Lower Confidence Limit**	**95% Upper Confidence Limit**
N	X.x					X.x (x.x)	X.xx	X.xx

[1] Lenth of engagement is calculated from the day of randomization to the last day a PILOT participant was assessed as “engaged” or “partially engaged” on the PIL form.

[2] Results are obtained from the Wald confidence limits.

17.1.7 Supportive Analyses of the Secondary Outcome

Table 38: Summary of Secondary Outcome Analysis: Steps Achieved Along a Modified SUD Cascade of Care by Primary Substance Use Disorder and Treatment Arm

Primary Substance of Use[1]	Number of Participants Randomized	Treatment Arm		Results[3]			
		TAU (N =XX)	PILOT (N =XX)				
		ORBC Score Collected at Day 180[2] (Mean (SD))	ORBC Score Collected at Day 180[2] (Mean (SD))	Rate Ratio	95% Lower Confidence Limit	95% Upper Confidence Limit	p-value
Primary OUD	N	X.X (X.XX)	X.X (X.XX)	X.XX	X.XX	X.XX	0.xxx
Primary SUD other than OUD							
No SUD identified at baseline							

[1] Primary substance of use is identified at baseline via the DSM-5 checklist.

[2] Steps achieved is collected on the following forms: HRC, SAA, MCA, DSM, UDT, and ARC

[3] Results are obtained from the longitudinal mixed effects model. The rate ratio and p-value result from the interaction term between treatment arm, SUD subgroup, and day at Day 180.

17.1.8 Safety Outcomes

Table 39: Summary of Hospitalizations by Treatment Arm

		Treatment Arm		
Study Period[1]		**TAU (N=XX)**	**PILOT (N=XX)**	**Total (N=XX)**
Treatment Period	Number of participants with at least one hospitalization[2]	N (X.x%)		
	Number of participants with at least one hospitalization related to substance use[3]	N(X.x%)		
	Related to overdose[4,5]			
	Related to withdrawal[4,5]			
	Related to intoxication[4,5]			
	Number of hospitalizations	N	N	N
	Number of hospitalizations per participant[2]			
	0			
	1			
	2			
	3			
	4			
	5 or more			
Follow-up Period	Number of participants with at least one hospitalization[2]			
	Number of participants with at least one hospitalization related to substance use[3]			
	Related to overdose[4,5]			
	Related to withdrawal[4,5]			
	Related to intoxication[4,5]			
	Number of hospitalizations			
	Number of hospitalizations per participant[2]			
	0			
	1			
	2			
	3			
	4			
	5 or more			

Hospitalizations are as captured on the ED Visits and Hospitalization (EDH) form.

[1] The treatment period extends from day of randomization to Study Day 180. After that, the follow-up day extends to Study Day 210.

[2] The percentage is calculated with the denominator as the number of participants randomized.

[3] The percentage is calculated with the denominator as the number of participants with at least one hospitalization.

[4] The percentage is calculated with the denominator as the number of participants with at least one hospitalization related to substance use.

[5] The hospitalization related to substance use may be due to multiple reasons.

Listing 1: Hospitalizations by Treatment Arm								
Treatment Arm = TAU								
Site	**Participant ID**	**Date of Randomization**	**Hospitalization Date**	**Discharge Date**	**Primary Diagnosis/ Complaint**	**Secondary Diagnosis/ Complaint**	**Tertiary Diagnosis/ Complaint**	**Outcome**
xxxxx	xxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxxx	xxxxxxxxx	xxxxxxxxx	Recovering/resolving Recovered/resolved Recovered/ resolved with sequelae Not recovered/not resolved Fatal Unknown

Listing 1: Hospitalizations by Treatment Arm								
Treatment Arm = PILOT								
Site	**Participant ID**	**Date of Randomization**	**Hospitalization Date**	**Discharge Date**	**Primary Diagnosis/ Complaint**	**Secondary Diagnosis/ Complaint**	**Tertiary Diagnosis/ Complaint**	**Outcome**
xxxxx	xxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxxx	xxxxxxxxx	xxxxxxxxx	Recovering/resolving Recovered/resolved Recovered/ resolved with sequelae Not recovered/not resolved Fatal Unknown

Table 40: Summary of ED Visits by Treatment Arm				
		Treatment Arm		
Study Period[1]		**TAU (N=XX)**	**PILOT (N=XX)**	**Total (N=XX)**
Treatment Period	Number of participants with at least one ED visit[2]	N (X.x%)		
	Number of participants with at least one ED visit related to substance use[3]			
	Related to overdose[4,5]			
	Related to withdrawal[4,5]			
	Related to intoxication[4,5]			
	Number of ED visits			
	Number of ED visits per participant[2]			
	0			
	1			
	2			
	3			
	4			
	5 or more			
Follow-up Period	Number of participants with at least one ED visit[2]			
	Number of participants with at least one ED visit related to substance use[3]			
	Related to overdose[4,5]			
	Related to withdrawal[4,5]			
	Related to intoxication[4,5]			
	Number of ED visits			
	Number of ED visits per participant[2]			
	0			
	1			
	2			
	3			
	4			
	5 or more			

ED Visits are as captured on the ED Visits and Hospitalization (EDH) form and do not include the index ED visit.

[1] The treatment period extends from day of randomization to Study Day 180. After that, the follow-up day extends to Study Day 210.

[2] The percentage is calculated with the denominator as the number of participants randomized.

[3] The percentage is calculated with the denominator as the number of participants with at least one ED visit.

[4] The percentage is calculated with the denominator as the number of participants with at least one ED visit related to substance use.

[5] The ED visit related to substance use may be due to multiple reasons.

Listing 2: ED Visits by Treatment Arm								
Treatment Arm = TAU								
Site	**Participant ID**	**Date of Randomization**	**ED Visit Date**	**Discharge Date**	**Primary Diagnosis/ Complaint**	**Secondary Diagnosis/ Complaint**	**Tertiary Diagnosis/ Complaint**	**Outcome**
xxxxx	xxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxxx	xxxxxxxxx	xxxxxxxxx	Recovering/resolving Recovered/resolved Recovered/ resolved with sequelae Not recovered/not resolved Fatal Unknown

Listing 2: ED Visits by Treatment Arm								
Treatment Arm = PILOT								
Site	**Participant ID**	**Date of Randomization**	**ED Visit Date**	**Discharge Date**	**Primary Diagnosis/ Complaint**	**Secondary Diagnosis/ Complaint**	**Tertiary Diagnosis/ Complaint**	**Outcome**
xxxxx	xxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxxx	xxxxxxxxx	xxxxxxxxx	Recovering/resolving Recovered/resolved Recovered/ resolved with sequelae Not recovered/not resolved Fatal Unknown

Table 41: Summary of Non-fatal Overdoses by Treatment Arm				
		Treatment Arm		
Visit		**TAU (N=XX)**	**PILOT (N=XX)**	**Total (N=XX)**
Baseline	Number of overdoses in the past 30 days	N		
	Number of participants with at least one overdose in the past 30 days	N (X%)		
	Number of overdoses per participant in the past 30 days			
	N	N		
	Mean	X.X		
	SD	X.XX		
	Min	X		
	25th Percentile			
	Median	X		
	75th Percentile			
	Max	X		
	Number of participants with at least one opioid overdose in the past 30 days	N (X%)		
	Number of overdoses with additional information in the past 30 days	N		
	NARCAN (naloxone) used to reverse overdose[1]			
	Don't know			
	No			
	Yes			
	Overdose resulting in treatment at an Emergency Department[1]			
	No			
	Yes			
	Overdose resulting in being admitted to the hospital[1]			
	No			
	Yes			
	Overdose involving opioids[1]			
	No			
	Yes			
	If opioid overdose, participant was trying to overdose[1,2]			
	No			
	Yes			

Table 41: Summary of Non-fatal Overdoses by Treatment Arm				
		Treatment Arm		
Visit		**TAU (N=XX)**	**PILOT (N=XX)**	**Total (N=XX)**
Day 30	Number of overdoses since last study visit			
	Number of participants with at least one overdose since last study visit			
	Number of overdoses per participant since last study visit			
	N			
	Mean			
	SD			
	Min			
	25th Percentile			
	Median			
	75th Percentile			
	Max			
	Number of participants with at least one opioid overdose since last study visit			
	Number of overdoses with additional information during this assessment period[1]			
	NARCAN (naloxone) used to reverse overdose[1]			
	Don't know			
	No			
	Yes			
	Overdose resulting in treatment at an Emergency Department[1]			
	No			
	Yes			
	Overdose resulting in being admitted to the hospital[1]			
	No			
	Yes			
	Overdose involving opioids[1]			
	No			
	Yes			
	If opioid overdose, participant was trying to overdose[1,2]			
	No			
	Yes			

Table 41: Summary of Non-fatal Overdoses by Treatment Arm				
		Treatment Arm		
Visit		TAU (N=XX)	PILOT (N=XX)	Total (N=XX)
Day 90	Number of overdoses since last study visit			
	Number of participants with at least one overdose since last study visit			
	Number of overdoses per participant since last study visit			
	N			
	Mean			
	SD			
	Min			
	25th Percentile			
	Median			
	75th Percentile			
	Max			
	Number of participants with at least one opioid overdose since last study visit			
	Number of overdoses with additional information during this assessment period[1]			
	NARCAN (naloxone) used to reverse overdose[1]			
	Don't know			
	No			
	Yes			
	Overdose resulting in treatment at an Emergency Department[1]			
	No			
	Yes			
	Overdose resulting in being admitted to the hospital[1]			
	No			
	Yes			
	Overdose involving opioids[1]			
	No			
	Yes			
	If opioid overdose, participant was trying to overdose[1,2]			
	No			
	Yes			
Day 180	Number of overdoses since last study visit			
	Number of participants with at least one overdose since last study visit			
	Number of overdoses per participant since last study visit			

Table 41: Summary of Non-fatal Overdoses by Treatment Arm				
		Treatment Arm		
Visit		**TAU (N=XX)**	**PILOT (N=XX)**	**Total (N=XX)**
	N			
	Mean			
	SD			
	Min			
	25th Percentile			
	Median			
	75th Percentile			
	Max			
	Number of participants with at least one opioid overdose since last study visit			
	Number of overdoses with additional information during this assessment period[1]			
	NARCAN (naloxone) used to reverse overdose[1]			
	Don't know			
	No			
	Yes			
	Overdose resulting in treatment at an Emergency Department[1]			
	No			
	Yes			
	Overdose resulting in being admitted to the hospital[1]			
	No			
	Yes			
	Overdose involving opioids[1]			
	No			
	Yes			
	If opioid overdose, participant was trying to overdose[1,2]			
	No			
	Yes			
Day 210	Number of overdoses since last study visit			
	Number of participants with at least one overdose since last study visit			
	Number of overdoses per participant since last study visit			
	N			
	Mean			
	SD			

Table 41: Summary of Non-fatal Overdoses by Treatment Arm				
		Treatment Arm		
Visit		**TAU (N=XX)**	**PILOT (N=XX)**	**Total (N=XX)**
	Min			
	25th Percentile			
	Median			
	75th Percentile			
	Max			
	Number of participants with at least one opioid overdose since last study visit			
	Number of overdoses with additional information during this assessment period[1]			
	NARCAN (naloxone) used to reverse overdose[1]			
	Don't know			
	No			
	Yes			
	Overdose resulting in treatment at an Emergency Department[1]			
	No			
	Yes			
	Overdose resulting in being admitted to the hospital[1]			
	No			
	Yes			

Overdoses as captured on the Overdose Information (ODI) form.

[1] Number of overdoses out of the up to two most recent overdoses collected per participant per visit.

[2] Percentage is based on the denominator of number of opioid overdoses.

Listing 3: Non-Fatal Overdoses by Treatment Arm											
Treatment Arm = TAU											
							Most Recent Overdoses[2]				
Site	Participant ID	Date of Randomization	Date of Assessment	Visit	Number of Overdoses[1]	Overdose Involving Opioids	Required NARCAN (naloxone) to Reverse Overdose	Required Treatment at an Emergency Department	Required Being Admitted to the Hospital	Substances Used	Participant was Trying to Overdose
xxxxx	xxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	Baseline/ Day 30/ Day 90/ Day 180/ Day 210	N	No/Yes	N	N	N	Opioids/ Benzodiazepines/ Cocaine/ Methamphetamine/ Alcohol/ Barbiturates/ Other: {specify]	No/ Yes

Overdoses as captured on the Overdose Information (ODI) form. All visits with ODI completed are included for participants who reported at least one overdose (excluding index overdose) at any visit.

[1] At baseline, number of overdoses in the past 30 days. At Day 30, Day 90, Day 180 and Day 210 visits, number of overdoses since last study visit.

[2] Number of overdoses out of the up to two most recent overdoses collected per participant per visit.

Listing 3: Non-Fatal Overdoses by Treatment Arm											
Treatment Arm = PILOT											
							Most Recent Overdoses[2]				
Site	Participant ID	Date of Randomization	Date of Assessment	Visit	Number of Overdoses[1]	Overdose Involving Opioids	Required NARCAN (naloxone) to Reverse Overdose	Required Treatment at an Emergency Department	Required Being Admitted to the Hospital	Substances Used	Participant was Trying to Overdose
xxxxx	xxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	Baseline/ Day 30/ Day 90/ Day 180/ Day 210	N	No/Yes	N	N	N	Opioids/ Benzodiazepines/ Cocaine/ Methamphetamine/ Alcohol/ Barbiturates/ Other: [specify]	No/ Yes

Overdoses as captured on the Overdose Information (ODI) form. All visits with ODI completed are included for participants who reported at least one overdose (excluding index overdose) at any visit.

[1] At baseline, number of overdoses in the past 30 days. At Day 30, Day 90, Day 180 and Day 210 visits, number of overdoses since last study visit.

[2] Number of overdoses out of the up to two most recent overdoses collected per participant per visit.

Table 42: Summary of Suicide Risk by Treatment Arm				
		Treatment Arm		
Visit	**Over the last two weeks, how often have you been bothered by thoughts that you would be better off dead, or of hurting yourself in some way?[1]**	**TAU (N=XX)**	**PILOT (N=XX)**	**Total (N=XX)**
Screening	Responses[2]			
	Not at all			
	Several days			
	More than half the days			
	Nearly every day			
Day 30	Responses[2]			
	Not at all			
	Several days			
	More than half the days			
	Nearly every day			
Day 90	Responses[2]			
	Not at all			
	Several days			
	More than half the days			
	Nearly every day			
Day 180	Responses[2]			
	Not at all			
	Several days			
	More than half the days			
	Nearly every day			
Day 210	Responses[2]			
	Not at all			
	Several days			
	More than half the days			
	Nearly every day			

[1] This question is asked as part of the 9-item version of the Patient Health Questionnaire (PHQ-9).

[2] The percentage of the number of responses is calculated with the number randomized as the denominator. The percentage for individual responses is calculated with the number of responses as the denominator.

Listing 4: Suicide Risk by Treatment Arm					
Treatment Arm = TAU					
Site	**Participant ID**	**Date of Randomization**	**Date of Assessment**	**Visit**	**Thoughts You are Better Off Dead or of Hurting Yourself[1]**
xxxxx	xxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	Screening/ Day 30/ Day 90/ Day 180/ Day 210	Not at all/ Several days/ More than half the days/ Nearly every day

[1] All visits with PHQ-9 completed are included for participants who indicate suicide risk at any visit. For PHQ-9 suicide risk is indicated by a response of “Several days”, “More than half the days” or “Nearly every day”.

Listing 4: Suicide Risk by Treatment Arm					
Treatment Arm = PILOT					
Site	**Participant ID**	**Date of Randomization**	**Date of Assessment**	**Visit**	**Thoughts You are Better Off Dead or of Hurting Yourself[1]**
xxxxx	xxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	Screening/ Day 30/ Day 90/ Day 180/ Day 210	Not at all/ Several days/ More than half the days/ Nearly every day

[1] All visits with PHQ-9 completed are included for participants who indicate suicide risk at any visit. For PHQ-9 suicide risk is indicated by a response of “Several days”, “More than half the days” or “Nearly every day”.

Listing 5: Deaths by Treatment Arm									
Treatment Arm = TAU									
							MedDRA V26.1		
Site	**Participant ID**	**Date of Randomization**	**Date of Death**	**Source of Death Report**	**Type**	**Cause of Death**	**Preferred Term**	**System Organ Class**	**Contributing Factors**
xxxxx	xxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	Medical chart/ Death certificate/ Autopsy report/ Treating physician/ Other	Primary/ Secondary	xxxxxxxxxxxxxx xxxxxxxxxxx	xxxxxxxxxxx xxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxx	Alcohol/Drug/ None/ Unknown

Listing 5: Deaths by Treatment Arm									
Treatment Arm = PILOT									
							MedDRA V26.1		
Site	Participant ID	Date of Randomization	Date of Death	Source of Death Report	Type	Cause of Death	Preferred Term	System Organ Class	Contributing Factors
xxxxx	xxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	Medical chart/ Death certificate/ Autopsy report/ Treating physician/ Other	Primary/ Secondary	xxxxxxxxxxxxxx xxxxxxxxxxxx	xxxxxxxxxxxx xxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxx	Alcohol/Drug/ None/ Unknown

17.1.9 Data Quality

Table 43: Summary of Data Audits

Site	Date of Audit	Total Fields Audited[1]	Total Data Discrepancies[2]	Error Rate
Site 1	mm/dd/yyyy	N	N	X.XX%
	Subtotal			
Site 2	mm/dd/yyyy			
	Subtotal			
Site 3	mm/dd/yyyy			
	Subtotal			
Total				

[1] Fields reviewed at monitoring visit comparing the database to source documentation.

[2] Fields discrepant between database and source documentation.

17.1.10 Protocol Deviations

Table 44: Summary of Protocol Deviations				
	Site 1	**Site 2**	**Site 3**	**Total**
Total number of protocol deviations	N			
Number of participants impacted per protocol deviation				
None	N (X%)			
One				
More than one				
Total number of major protocol deviations	N			
Type of major protocol deviation				
No consent/assent obtained	N (X%)			
Unauthorized assessments and/or procedures conducted prior to obtaining informed consent/assent				
Non-IRB approved/outdated/obsolete informed consent/assent documents				
Ineligible participant randomized/inclusion/exclusion criteria not met or eligibility not fully assessed prior to randomization				
Study assessments/procedures not followed in accordance with the study protocol				
Stratification error				
Study behavioral intervention was not provided/performed as per protocol				
Safety event not reported				
Safety event reported out of protocol specified reporting timeframe				
Safety event not elicited, observed and/or documented as per protocol				
Safety event assessment not conducted per protocol				
Destruction of study materials without prior authorization from sponsor				

Table 44: Summary of Protocol Deviations				
	Site 1	**Site 2**	**Site 3**	**Total**
Breach of Confidentiality				
Other informed consent/assent procedures issues				
Other inclusion/exclusion criteria issues				
Other laboratory assessments issues				
Other study procedures/assessments issues				
Other randomization procedures issues				
Other study behavioral intervention issues				
Other safety event issues				
Other significant deviations issues				
Total number of minor protocol deviations	N			
Type of minor protocol deviation				
No consent/assent obtained	N (X%)			
Unauthorized assessments and/or procedures conducted prior to obtaining informed consent/assent				
Non-IRB approved/outdated/obsolete informed consent/assent documents used				
Ineligible participant randomized/inclusion/exclusion criteria not met or eligibility not fully assessed prior to randomization				
Study assessments/procedures not followed in accordance with the study protocol				
Stratification error				
Study behavioral intervention was not provided/performed as per protocol				
Safety event not reported				
Safety event reported out of protocol specified reporting timeframe				
Safety event not elicited, observed and/or documented as per protocol				

Table 44: Summary of Protocol Deviations				
	Site 1	**Site 2**	**Site 3**	**Total**
Safety event assessment not conducted per protocol				
Destruction of study materials without prior authorization from sponsor				
Breach of Confidentiality				
Other inclusion/exclusion criteria issues				
Other laboratory assessments issues				
Other study procedures/assessments issues				
Other randomization procedures issues				
Other study behavioral intervention issues				
Other safety event issues				
Other significant deviations issues				

Listing 6: Protocol Deviations												
Deviation Category = Informed Consent Procedures												
Site	**Related Participant IDs**	**Date of Protocol Deviation**	**Date Protocol Deviation Entered in EDC**	**Deviation Type**	**Reason for Protocol Deviation**	**Related to COVID-19?**	**Deviation Description**	**Will Corrective Action be Taken?**	**Plan to Prevent Recurrence**	**IRB Reporting Required?**	**IRB Notified at Continuing Review?**	**Date of Planned/ Actual IRB Report**
xxxxxxx	xxxxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxx	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	Yes/No	mm/dd/yyyy

Listing 6: Protocol Deviations												
Deviation Category = Inclusion/Exclusion Criteria												
Site	**Related Participant IDs**	**Date of Protocol Deviation**	**Date Protocol Deviation Entered in EDC**	**Deviation Type**	**Reason for Protocol Deviation**	**Related to COVID-19?**	**Deviation Description**	**Will Corrective Action be Taken?**	**Plan to Prevent Recurrence**	**IRB Reporting Required?**	**IRB Notified at Continuing Review?**	**Date of Planned/ Actual IRB Report**
xxxxxxx	xxxxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxx	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	Yes/No	mm/dd/yyyy

Listing 6: Protocol Deviations												
Deviation Category = Laboratory Assessment												
Site	**Related Participant IDs**	**Date of Protocol Deviation**	**Date Protocol Deviation Entered in EDC**	**Deviation Type**	**Reason for Protocol Deviation**	**Related to COVID-19?**	**Deviation Description**	**Will Corrective Action be Taken?**	**Plan to Prevent Recurrence**	**IRB Reporting Required?**	**IRB Notified at Continuing Review?**	**Date of Planned/ Actual IRB Report**
xxxxxxx	xxxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxx	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	Yes/No	mm/dd/yyyy

Listing 6: Protocol Deviations												
Deviation Category = Study Procedures/Assessments												
Site	**Related Participant IDs**	**Date of Protocol Deviation**	**Date Protocol Deviation Entered in EDC**	**Deviation Type**	**Reason for Protocol Deviation**	**Related to COVID-19?**	**Deviation Description**	**Will Corrective Action be Taken?**	**Plan to Prevent Recurrence**	**IRB Reporting Required?**	**IRB Notified at Continuing Review?**	**Date of Planned/ Actual IRB Report**
xxxxxxx	xxxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxx	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	Yes/No	mm/dd/yyyy

Listing 6: Protocol Deviations												
Deviation Category = Randomization Procedures												
Site	**Related Participant IDs**	**Date of Protocol Deviation**	**Date Protocol Deviation Entered in EDC**	**Deviation Type**	**Reason for Protocol Deviation**	**Related to COVID-19?**	**Deviation Description**	**Will Corrective Action be Taken?**	**Plan to Prevent Recurrence**	**IRB Reporting Required?**	**IRB Notified at Continuing Review?**	**Date of Planned/ Actual IRB Report**
xxxxxxx	xxxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxx	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	Yes/No	mm/dd/yyyy

Listing 6: Protocol Deviations												
Deviation Category = Study Behavioral Intervention												
Site	**Related Participant IDs**	**Date of Protocol Deviation**	**Date Protocol Deviation Entered in EDC**	**Deviation Type**	**Reason for Protocol Deviation**	**Related to COVID-19?**	**Deviation Description**	**Will Corrective Action be Taken?**	**Plan to Prevent Recurrence**	**IRB Reporting Required?**	**IRB Notified at Continuing Review?**	**Date of Planned/ Actual IRB Report**
xxxxxxx	xxxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxx	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	Yes/No	mm/dd/yyyy

Listing 6: Protocol Deviations												
Deviation Category = Safety Event												
Site	**Related Participant IDs**	**Date of Protocol Deviation**	**Date Protocol Deviation Entered in EDC**	**Deviation Type**	**Reason for Protocol Deviation**	**Related to COVID-19?**	**Deviation Description**	**Will Corrective Action be Taken?**	**Plan to Prevent Recurrence**	**IRB Reporting Required?**	**IRB Notified at Continuing Review?**	**Date of Planned/ Actual IRB Report**
xxxxxxx	xxxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxx	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	Yes/No	mm/dd/yyyy

Listing 6: Protocol Deviations												
Deviation Category = Other Significant Deviation												
Site	**Related Participant IDs**	**Date of Protocol Deviation**	**Date Protocol Deviation Entered in EDC**	**Deviation Type**	**Reason for Protocol Deviation**	**Related to COVID-19?**	**Deviation Description**	**Will Corrective Action be Taken?**	**Plan to Prevent Recurrence**	**IRB Reporting Required?**	**IRB Notified at Continuing Review?**	**Date of Planned/ Actual IRB Report**
xxxxxxx	xxxxxxxxxxxxxx	mm/dd/yyyy	mm/dd/yyyy	xxxxxxxx	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	xxxxxxxx	Yes/No	Yes/No	mm/dd/yyyy