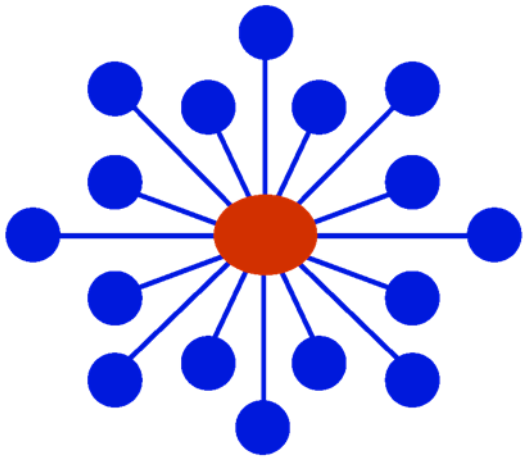

NIDA CTN Protocol 0107

Peer Intervention to Link Overdose Survivors to Treatment (PILOT)

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Sponsor: National Institute on Drug Abuse (NIDA)

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CONFIDENTIAL

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CONFIDENTIALITY STATEMENT

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1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ASI-Lite	Addiction Severity Index-Lite
CCC	Clinical Coordinating Center
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Act
CoC	Certificate of Confidentiality
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
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HER	Electronic Health Record
HIPAA	Health Insurance Portability and Accountability Act
HSP	Human Subjects Protection
ICF	Informed Consent form
IRB	Institutional Review Board
ITT	Intention To Treat
LI	Lead Investigator
MOP	Manual of Procedures
MOUD	Medication for Opioid Use Disorder
MUSC	Medical University of South Carolina
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
PhenX	Phenotypes and Exposures
PILOT	Peer Intervention to Link Overdose survivors to Treatment
QA	Quality Assurance
RA	Research Assistant
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SBIRT	Screening, Brief Intervention and Referral to Treatment
SD	Standard Deviation
SDS	Saliva Drug Screen
SUD	Substance Use Disorder
TAU	Treatment As Usual
TLFB	Timeline Follow-Back

2.0 STUDY SYNOPSIS

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 vs 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).

2.2 Study Design and Outcomes

This is a multi-site, prospective, randomized, controlled pilot trial comparing the PILOT intervention with Treatment as Usual (TAU) on the frequency of self-reported overdose risk behaviors for those who survive a NFOO and present to the ED.

The first aim of this study is to test the hypothesis that PILOT will lead to a reduced frequency of self-reported overdose risk behaviors among NFOO survivors at 180 days (end of treatment) compared to TAU (primary outcome measure).

The secondary aims of the study are to: 1) evaluate the number of steps achieved along a modified SUD Cascade of Care among individuals with a recent NFOO, and 2) assess whether NFOO survivors within an ED setting are willing to engage in study procedures and with peer support specialists, measured by (a) the number of potentially eligible patients approached compared with the number willing to be enrolled, and (b) the length of engagement and enrollment in PILOT among those willing to be enrolled and randomized to PILOT.

2.3 Sample Size and Study Population

A total of approximately 150 eligible patients (ages 18+) who have been identified as having a recent NFOO in the ED 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.

2.4 Treatment, Assessment, Intervention, and Duration

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. After screening and consent, 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 (referred to as Certified Peer Support Specialist [CPSS] in South Carolina but may have other official titles in other states) 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. TAU participants will also meet separately with the research staff to complete study assessments, including a 210-day (7-month) follow-up visit after the 180-day (6-month) intervention window has closed.

Those randomized to the PILOT intervention will continue with routine clinical treatment as provided in that ED (including the TAU peer as available) *and* meet with 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 of both approaches. 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).

Given potential access restrictions to EDs due to the COVID-19 pandemic, contingency plans are in place should access to the ED be restricted for peers and research staff at any time during study enrollment to engage patients remotely and conduct consent and all study procedures remotely.

Research follow-up visits will occur at 30, 90, 180, and 210 days after randomization to PILOT or TAU, with the day of randomization being considered study Day 0. Follow-up 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 through the study for the duration of the study and follow-up period to complete surveys and provide a means of communication with research staff.

Those who decline to participate in the study will receive TAU as provided in that ED setting and will have the option to fill out a brief de-identified survey to elucidate characteristics of suspected overdose and reasons for study decline.

2.5 Safety Reporting

Given the low-risk nature of the PILOT intervention, only targeted Safety Event reporting will be conducted during this study. Specifically, deaths, post-index visit overdoses, suicidal ideation, Emergency Department (ED) visits, and hospitalizations will be solicited during the 30-, 90-, 180-, and 210-day visits (or in-between visits if reported spontaneously). Reporting timeframes for these targeted Safety Events will follow regulatory requirements. While active suicidal ideation at the

screening/baseline visit is considered an exclusion criterion, participant suicidal ideation occurring after enrollment will be addressed in accordance with **Section 11.7.1**.

For the purposes of this protocol, the following events do not require reporting in the data system:

- Pregnancy
- Admission for detoxification
- Elective hospitalization

2.6 Analyses

The primary outcome, frequency of self-reported overdose risk behaviors, will be compared between TAU and PILOT treatment groups at the 180-day end-of-treatment study visit and will be analyzed via a mixed effect Poisson regression model with fixed effect covariates including baseline frequency, treatment, site, days, and the stratifying variable. A random effect for participant is included. Treatment effect is measured by a rate ratio (RR) from the model, interpreted as the ratio of the mean frequency of self-reported overdose risk behaviors for PILOT to TAU, conditional on all over covariates being equal (including baseline frequency), at 180 days. A RR value of less than 1 indicates a lower mean frequency for PILOT as compared to TAU.

3.0 STUDY SCHEMA

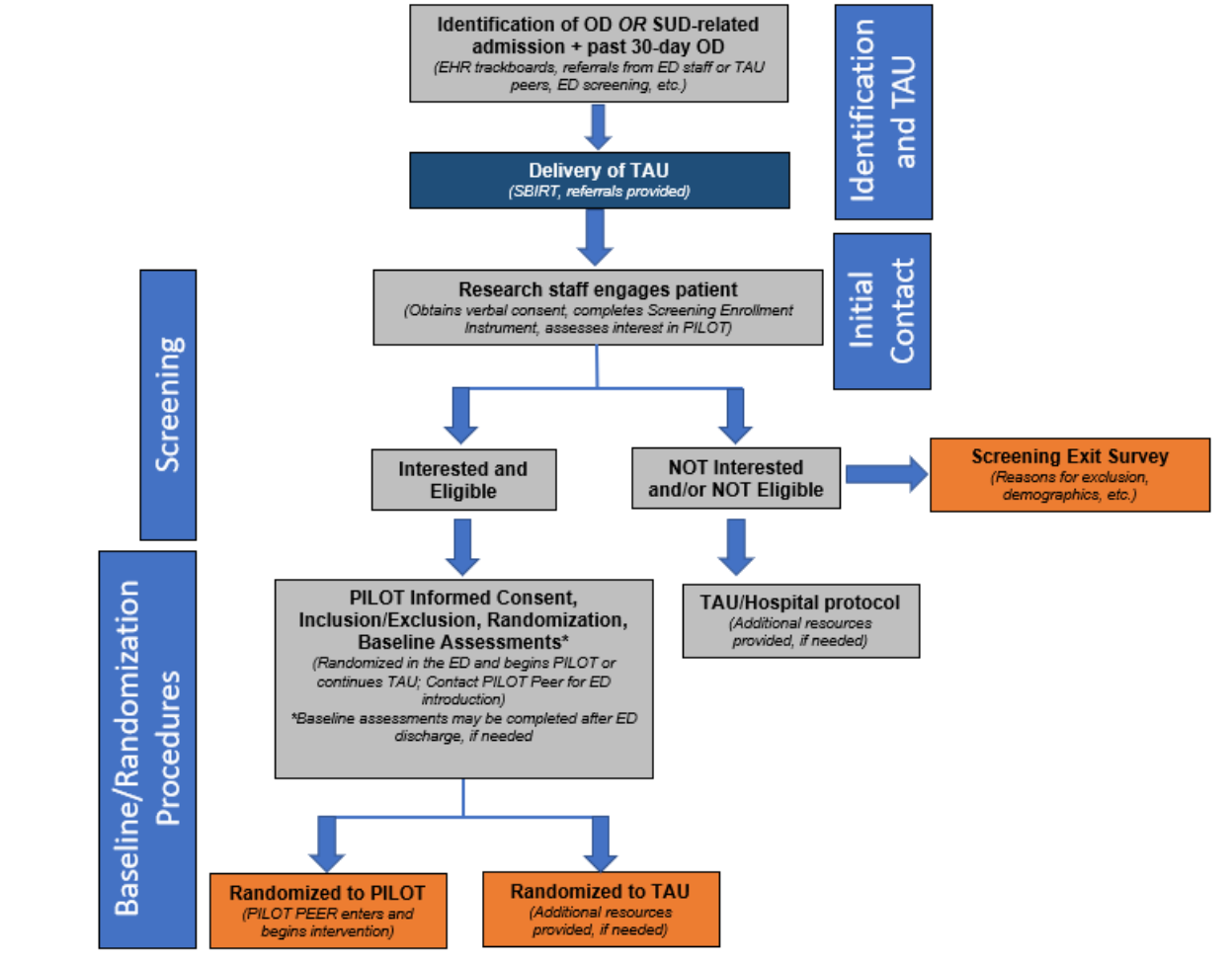


Figure 1: Schema to identify potential study participants, engage the participant, assess interest in the study, screen, and enroll study participants into CTN-0107 as part of in-person ED procedures. This figure does not display the process of identification of patients and enrollment, should access to the ED be restricted. Those plans are described below. TAU is delivered to all study participants, including PILOT participants.

3.1 Key Research Site Roles

Site Principal Investigator/Site Director

PILOT Peers (Certified Peer Support Specialists trained to deliver the PILOT intervention)

PILOT Lead Peer

Research Coordinator/Research Assistant

4.0 INTRODUCTION

4.1 Background and Significance to the Field

The alarming increase in number of overdose deaths globally [1] and in the United States (US) specifically over the past decade has led to a decrease in average life expectancy for the nation [2]. One of the greatest risk factors for overdose death is experiencing a non-fatal overdose involving opioids (NFOO) in the previous year, with estimates of 5.5% [3] to 10% [4] of individuals experiencing an NFOO dying within the next year. NFOO survivors most commonly die of another overdose (67%, average age 39) [3], with the highest risk period being the month following NFOO [5].

With over 140,000 visits to Emergency Departments (EDs) per year for non-fatal overdoses in the US [4], the ED setting provides a reachable moment for intervention in this population [6, 7]. However, although successful medical interventions have been implemented across the nation to broaden the initiation of medications for opioid use disorder (MOUD) in the ED [8], which is known to decrease mortality for those with OUD [9, 10], NFOO survivors have low rates of treatment engagement, with only 34% engaging in substance use disorder (SUD) treatment in the year after NFOO [3].

The reasons for low engagement in SUD treatment after NFOO are multifactorial. In addition to low motivation for treatment in some and barriers to treatment engagement (e.g., financial and logistical) in individuals motivated for treatment [11], it is known that only 47% of those experiencing a NFOO have a *known diagnosis* of SUD, with only 27% having an OUD diagnosis [12]. Additionally, 78% have a co-occurring mental health diagnosis [11], which further complicates management. Whether OUD is being under-detected in this population or not detected at all, or whether this population is under-reporting OUD, has a primary SUD other than OUD, has primary mental health issues other than SUD, or a combination of these factors, is not well described. Given the low numbers of individuals with reported OUD in this population, it is not surprising that traditional addiction medicine approaches, including those focused on initiating MOUD, result in low treatment engagement for NFOO survivors [11], and misses a prime opportunity to intervene with the appreciable proportion of those for whom MOUD is not indicated or desired, yet who remain at high risk.

Given that almost half of NFOO survivors self-report *not* having substance problems involving opioids [11], a peer-led support and risk reduction intervention that does *not* initially focus on MOUD engagement or engagement in formal SUD treatment is desirable in this population. Peer support specialists who are trained in overdoses and risk mitigation strategies can utilize a multitude of non-medication approaches to engage NFOO survivors in behaviors that decrease risk for repeat overdose and increase entry into risk-reduction and recovery-based activities during the time for highest increased overdose risk, even if MOUD is not desired nor indicated. Additionally, by keeping in contact with NFOO survivors over time, utilizing motivational interviewing approaches, peer support specialists can be available to individuals if and when they become ready to engage in formal SUD treatment or higher levels of care.

Interventions targeting the post-NFOO population have grown in the past several years [13-17]. Acknowledging that the post-NFOO population tends to be more difficult to engage with traditional medical approaches, several states have developed peer-led ED interventions to increase treatment engagement. Although observational results of these pilot programs have been promising [13-15, 17], few have been systematically evaluated. One such program that has shown preliminary promise, developed through Faces and Voices of Recovery (FAVOR) in Greenville, South Carolina (SC), is FAVOR Overdose Recovery Coaching Evaluation (FORCE).

FORCE is an innovative program using Certified Peer Support Specialists (CPSSs, specific to South Carolina) specially trained in overdose, who are called to the ED as soon as an overdose survivor is admitted and identified. The mission of FORCE is to engage overdose survivors in whatever level of contact and care is acceptable (i.e., ride home, cup of coffee, formal treatment). The underlying philosophy of the program is grounded in motivational interviewing, case-management, health coaching, and assertive community engagement principles. The model resembles Strengths Based Case Management Approach to Patient Navigation used successfully in CTN-0049 (HOPE trial) to engage patients, coordinate care, assist patients to overcome personal barriers, and provide psychosocial and emotional support [18]. Strengths Based Case Management has been used effectively to assist individuals linking into as well as maintaining substance use treatment.

In FORCE, the CPSS typically meets the NFOO survivor in the ED and assumes responsibility for follow-up after ED discharge. The FORCE CPSS takes on significant responsibility for remaining in contact with clients, using a tiered approach, including text, phone, and in-person contact. The goal of the outreach is *engagement* and linkage to appropriate treatment (SUD or otherwise, largely based on the needs and preferences of the client at that time). A recent study evaluated a similar peer recovery coaching intervention among those who were hospitalized due to complications associated with their substance use [19] and found impressive rates of treatment engagement six months post discharge (84% vs. 34% in the control condition). While this study shows preliminary promise for intensive peer coaching and assertive community engagement, this intervention has not yet been evaluated among those presenting the ED with a NFOO who may not meet criteria for an SUD or OUD (up to 50% of those presenting with an NFOO).

Through the proposed multi-site, randomized, controlled pilot study, the study will assess the preliminary effectiveness and feasibility of a modified and manualized version of the FORCE model, PILOT, on overdose risk behaviors (as defined by an overdose risk behavior assessment) and treatment engagement, utilizing a modified SUD Cascade of Care model [20].

4.2 Study Rationale

For those with OUD, it is known that engagement in OUD treatment, longer retention in OUD treatment, and utilization of medication is associated with improved outcomes and decreased risk of subsequent overdose [9, 10]. After an NFOO, there is an initial increased likelihood of SUD treatment entry and utilization of buprenorphine. However, even at peak rates of treatment engagement – 11% at 1 month for SUD treatment engagement and 3% at 3 months for buprenorphine treatment – engagement is low and decreases with each additional month after overdose [12]. Moreover, given that less than half of the NFOO population identifies as having an

OUD, this low level of treatment entry and decline in treatment utilization over time raises the critical question of what treatment or risk reduction measures are appropriate for NFOO survivors, especially those for whom MOUD is not desired nor indicated, and how to improve the retention of those with SUD who enter treatment after an overdose [21, 22]. The proposed peer-led intervention being tested in this study (PILOT) has a distinct advantage in that it can assess and address overdose risk factors for those who survive an NFOO regardless of whether the individual identifies as having an SUD or is interested or ready for treatment entry.

Like similar programs [13-15, 17], FORCE has demonstrated remarkable preliminary success in observational evaluations, with linkage to treatment for 61% of participants in the first 18 months. As part of program evaluation for FORCE, in total, 235 overdose survivors have been approached, and 98% (n=230) agreed to participate in FORCE services, suggesting that recruiting overdose survivors from the ED utilizing this model is feasible. Fifty-eight percent of engaged clients (133/230) remained actively retained in FORCE at 9 months, defined as at least a monthly check in. Sixty-one percent (140/230) were linked with treatment or other recovery support services at some point in time during enrollment. Eight percent of engaged clients reported a return to any hospital “for any reason” (n=19), and 1.6% died of accidental overdose.

These encouraging observational results highlight the need for a more rigorous randomized controlled trial of peer-led engagement in risk reduction and treatment after overdose and presentation in the ED. While promising, the FORCE intervention has not been adequately tested for efficacy, which is the goal of the current trial. To conduct a preliminary test of a peer-led support intervention for overdose survivors (PILOT), participants randomized to PILOT will receive 6 months of peer support services via the PILOT intervention manual, with a 7-month follow-up visit to determine the initial durability of the intervention. The timeframe will aid in determining preliminary effectiveness, while also allowing for feasibility of study enrollment and recruitment. This pilot randomized controlled trial will test the preliminary effectiveness of a peer-overdose specialist-led intervention in the ED and allow for effect size determination for a larger randomized controlled trial.

5.0 PRIMARY AIMS, OBJECTIVES, AND HYPOTHESES

5.1 Overview

This study is a 2-arm randomized, prospective pilot trial comparing the effectiveness of PILOT with TAU on frequency of self-reported overdose risk behaviors for participants who present to an ED after a non-fatal overdose involving opioids (NFOO).

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.

The study will evaluate the frequency of self-reported overdose risk behaviors using a 13-item self-report survey (11 items used to generate a total score; 0-44 possible points) originally modified from a 9-item questionnaire utilized in a pilot randomized controlled trial in a similar population [23] and currently being used in the CTN-0101 STOP trial. The modified 11-item version is currently being used in a current randomized controlled trial of a post-overdose intervention in New York City (clinical trials.gov identifier: NCT04317053). The questionnaire was developed and modified based on known factors associated with risk for overdose, including more current overdose risk factors such as fentanyl use [23-33]. The questions measure the frequency (over a specified time frame) at which individuals used drugs alone; used in a new place/environment; used other substances (alcohol, benzodiazepines, stimulants) within two (2) hours of opioids; used more than one opioid; used more than the usual amount; and used inhaled or injected opioids.

The study will also secondarily evaluate treatment engagement utilizing a modified SUD Cascade of Care, developed for this study, which outlines 10 steps representing different stages of SUD treatment engagement ranging from harm reduction to engagement in SUD treatment to improvement in recovery scores (see **Section 7.0**, **Outcome Measures**). These steps are not necessarily sequential nor contingent upon previous steps, but can assess for both informal and formal treatment engagement.

The aims and outcomes of this study are listed below. It should be noted that primary and secondary outcomes will be prioritized for publication following study enrollment. Exploratory aims will not prevent primary or secondary aims from being disseminated. Additional exploratory aims may be possible for analysis after publication of the primary and secondary aims of this trial.

5.2 Primary Aim

The primary aim of this study is to compare the effectiveness of PILOT versus TAU in approximately 150 patients who present to an ED after a recent NFOO on the outcome of the past month total score on the modified and expanded Overdose Risk Behavior Checklist at 180 days (6 months post-randomization).

5.3 Secondary Aims

The secondary aims of the study are to: 1) test the hypothesis that PILOT will result in a differing number of steps achieved on a modified SUD Cascade of Care at 180 days (6 months) after Index ED admission (Secondary Outcome Measure) as compared with TAU; and (2) assess whether recent NFOO survivors within an ED setting are willing to engage with peer support services, measured by (a) the number of potentially eligible patients approached compared with the number willing to be enrolled, and (b) the length of engagement and enrollment in PILOT among those willing to be enrolled and randomized to PILOT (Secondary Outcome Measure).

5.4 Exploratory Aims

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.

Exploratory Aim 2: To evaluate the effectiveness of PILOT versus TAU on initiation on MOUD in the ED for those with OUD (yes/no; assessed via self-report upon ED discharge or in follow-up assessment if unable to be assessed at ED discharge).

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)].

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 number of contacts received or initiated with a Peer Support Specialist in the past month (phone, video, or in-person).

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 (phone, video, or in-person).

Exploratory Aim 6: To evaluate the effectiveness of PILOT versus TAU on the percentage of toxicology screens positive for primary substance of use at 30-, 90-, 180-, and 210-days post-randomization.

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

6.0 STUDY DESIGN

6.1 Overview of Study Design

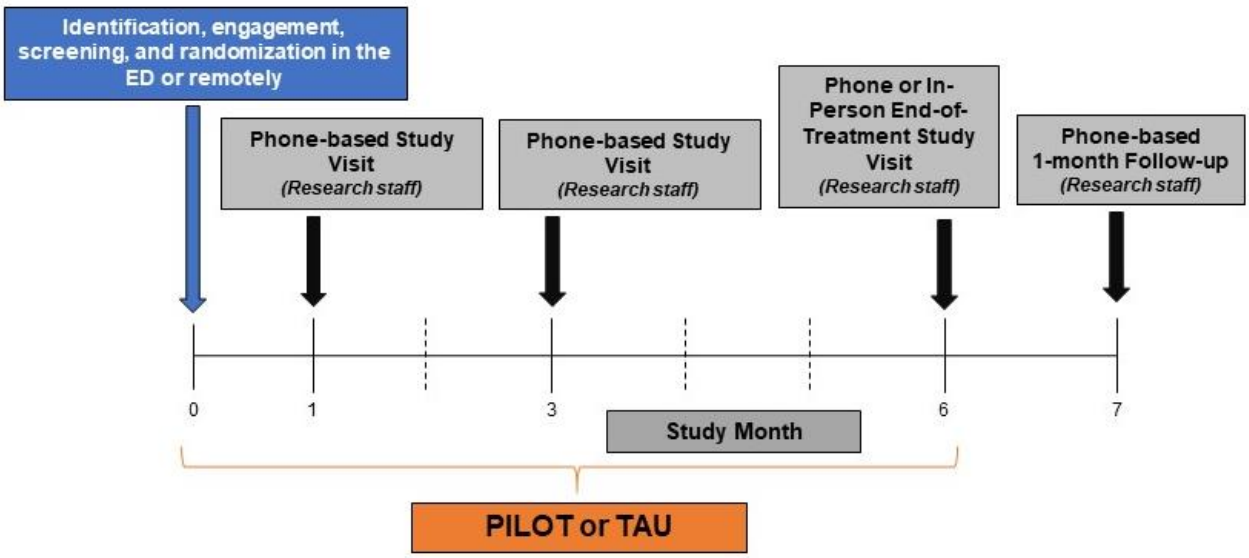


Figure 2: Study design. Additional information about the box in blue (identification and enrollment of study participants) can be found in Figure 1 above.

This is a 2-arm, multi-site, randomized, controlled trial evaluating the effectiveness of PILOT compared with TAU on the frequency of self-reported overdose risk behaviors at 180 days (6 months).

This study will be initiated in the Emergency Department (ED). In addition to routine ED medical care, all ED sites will have an operationalized peer support system in the ED that will serve as part of TAU ("TAU peer," though it should be noted that TAU peers may not be available 24 hours/day).

After assessment and stabilization as part of routine TAU by ED staff, a member of the research team will approach patients who may qualify for the study, in-person or remotely, for screening, consent, and enrollment in the study. All study sites will have detailed procedures for proper identification and recruitment of study participants. All study sites will operate under the MUSC policies and procedures for recruitment given the SmartIRB master reliance agreement. As such, recruitment procedures will be the same across study sites, with any differences outside of the MUSC policies being specifically stated and approved as part of local study site standard operating procedures (SOPs). If the participant is eligible and interested, after consent and determination of eligibility, they will be randomized to either PILOT (in addition to continuing TAU) or to continue TAU at that time.

For participants randomized to PILOT, in addition to receiving TAU (including possible interaction with the TAU peer), there will be an "on-call" system for the PILOT intervention peers such that

they are available to come to the ED to connect with any recent overdose survivors randomized to PILOT, either in-person or remotely. If these procedures are completed remotely, HIPAA-secure videoconferencing and approved REDCap tele-consenting will be used, and options will exist to complete screening and consent after a patient is discharged from the ED, should the potential participant provide verbal consent to be contacted by research staff about the study later . Intervention participants will begin the PILOT intervention in the ED, in-person or remotely, following the PILOT intervention manual. PILOT will utilize a tiered approach to assertive community engagement, utilizing motivational interviewing and Strengths-Based Case Management approach to engage patients in care and develop a patient-centered wellness/recovery plan. The PILOT intervention will be tailored to the participant's needs (e.g., harm reduction, recovery, and treatment resources as they are interested and ready) and will involve contact and interaction with PILOT peers (details included in the PILOT intervention manual) over the course of the 180-day (6 month) treatment period. Participants randomized to TAU will continue TAU and receive any additional standard treatment provided at the respective ED for overdose survivors, including interaction with TAU peer as per hospital practice. All participants (TAU and PILOT) will, in the least, 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. Addiction services can include a range of treatments with varying intensity and duration, based on local resources and patient preference. TAU peers will conduct their standard TAU protocol as they would for any other NFOO or substance use patient admitted to the ED, like what is described above as an SBIRT-like model common in hospital and ED settings with peer support services in place.

During the site selection process, a thorough assessment will be conducted of each site's standard practice for overdoses and substance-related issues in the ED and description of peer services will be provided and reviewed (See **Section 9.3**).

Throughout the course of the trial, sites will be monitored for any potential changes that might occur to TAU around providing resources and/or treatment to overdose survivors.

6.2 Duration of Study and Visit Schedule

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. Participants will be assessed at screening/baseline and at 30, 90, 180, and 210 days after randomization. This study is expected to last approximately 3 years, including site initiation and close-out activities.

Rationale for Study Duration and Visit Schedule: The purpose of this pilot randomized controlled trial (RCT) is to determine the preliminary effectiveness of PILOT, including feasibility of enrollment, engagement, follow-up and retention, follow-up procedures and preliminary duration of effect, if effective. Should PILOT be feasible and show preliminary effectiveness compared with TAU, an effect size will be determined and used to inform a larger and longer RCT to assess

replicability, generalizability, intervention dosing, and duration of effect after the intervention is completed.

Study visits are scheduled at 30, 90, 180 and 210 days. Based on preliminary results from the FORCE program and previously published outcomes with inpatients [19], the study hypothesis is that 180 days is an adequate period for most participants to demonstrate some benefit from this type of intervention. However, it is known that early recovery can be a time of lapses, disengagement, and re-engagement. The 30- and 90-day assessments allow for evaluation of participants who may be early responders and follow them over time to determine duration and pattern of engagement. Alternatively, some participants might take several months to enter and stabilize in recovery, and the overdose risk behavior scale and modified SUD Cascade of Care allow for measurement of earlier incremental or finite achievements within the 180-day intervention period to provide time for those with ambivalence and/or a disengagement/re-engagement pattern to demonstrate progress.

7.0 OUTCOME MEASURES

7.1 Primary Outcome Measure

The Primary Aim of this study is to compare the effectiveness of PILOT versus TAU in approximately 150 patients who are admitted to an ED after an NFOO or admitted to the ED with an SUD-related issue and self-report recent (past 30-day) NFOO on the primary outcome of the past month total score on the modified and expanded Overdose Risk Behavior Checklist, which captures the frequency of self-reported overdose risk behaviors, at 180 days (6 months). The study will use a modified and expanded version of an Overdose Risk Behavior Checklist (ORBC), adapted from Bohnert et al. (2016) [23]. This assessment has been adapted and is being used currently in a study focused on risk reduction in NFOO admissions to EDs (RELAY; NCT04317053). The ORBC that will be used in CTN-0107 is a 13-item scale, with 11 of the items used to generate a total score (ranging from 0-44); higher scores will indicate greater frequency and number of overdose risk behaviors. Some items have branching/sub questions, which are not included in the total score to allow for the same possible number of points for all study participants. These questions will measure risk behaviors in the past month, and the total risk score is an aggregation of responses to the specific individual questions.

7.1.1 Hypothesis 1 (Primary Outcome Measure):

The study hypothesis is that the PILOT intervention will result in reduced frequency of self-reported overdose risk behaviors (i.e., lower ORBC total score) via the ORBC at Day 180 after randomization compared to TAU.

7.2 Secondary Outcome Measures

The secondary outcomes of the study are: 1) number of steps achieved on a modified SUD Cascade of Care at 180 days (6 months) after Index ED admission; and (2) engagement with the study and PILOT intervention, measured by (a) the number of potentially eligible patients approached compared with the number willing to be enrolled and (b) the length of engagement and enrollment in PILOT among those randomized to PILOT. Length of engagement and enrollment is defined as the time from baseline to last meeting with the PILOT intervention/ counselor.

Modified SUD Cascade of Care (Secondary Outcome Measure):

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	Harm Reduction Checklist	Step 2-7 Assessment Form (SAF 2-7)		SAF 2-7	SAF 2-7 AND MOUD Confirmation Form			DSM 5 Checklist Toxicology screen		Assessment of Recovery Capital Scale

Step Eligibility: All enrolled participants will be considered to have 0 steps achieved at the time of study entry (baseline). Acknowledging that individuals will vary in presence and types of SUD diagnoses, this pilot trial will evaluate the differing numbers of steps achieved in each sub-type of enrolled participant (primary OUD, primary SUD other than OUD, no identified SUD identified at baseline via administration of the DSM-5 checklist). 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.

7.2.1 Hypothesis 2 (Secondary Outcome Measure)

PILOT will result in a differing number of steps achieved along the SUD Cascade of Care at 180 days after Index ED admission as compared with TAU. 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 *Harm Reduction Checklist* assessment: (1) any unchecked 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.

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 Steps 2-7 Assessment Form): (a) scheduling a formal SUD treatment appointment; (b) attending an in-person or on-line recovery or 12-step meeting (AA, NA, SMART, Celebrate Recovery, In the Rooms, etc.); (c) attending an in-person, virtual or phone session with a peer recovery specialist; (d) attending at an in-person or virtual formal SUD treatment appointment (medication and/or psychosocial treatment, including outpatient, intensive outpatient or residential treatment). Step 2 will be assessed throughout the 6-month treatment and 7-month 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 180 days), 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 Step 2 b-d activities at least 3 times in the past 90 days. 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.

4. Taking MOUD – Any: A participant will have attained Step 4 (after baseline assessment) if they self-report taking any dose of MOUD (no confirmation needed, but self-report of at least one dose). 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 AND toxicology screen(s) are positive for buprenorphine or methadone, consistent with self-report, as confirmed at study visits. 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 (e.g., a participant did not take MOUD in past 10 days, but did take MOUD the previous 20 days), Step 5 can also be confirmed by either (a) confirmation with treatment provider or pharmacy of prescription written and/or dispensed consistent with MOUD availability 20 of the past 30 days; 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). 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 AND toxicology screen(s) are positive for buprenorphine or methadone, 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 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, 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 180-day study visit.

8. Decrease SUD Severity: A participant will achieve Step 8 if the number of current SUD criteria met on the DSM-5 Checklist for the primary SUD decreases as compared with baseline at the 30-, 60- OR 180-day 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 on the DSM-5 Checklist AND has a toxicology screen negative for that substance at 30-day and 90-day OR 90-day and 180-day study visit. 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) scale [34] (range 0-50) increases by a value equivalent to 0.5 standard deviations within the validation sample, which was 11.54 [22] (5.77 point increase or greater needed to meet Step 10), from baseline to the 30- 90- OR 180-day visit. 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.

7.3 Other Outcome Measures

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.

Exploratory Aim 2: To evaluate the effectiveness of PILOT versus TAU on initiation on MOUD in the ED for those with OUD (yes/no; assessed via self-report upon ED discharge or in follow-up assessment if unable to be assessed at ED discharge).

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)].

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 number of contacts received or initiated with a Peer Support Specialist in the past month (phone, video, or in-person).

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 (phone, video, or in-person).

Exploratory Aim 6: To evaluate the effectiveness of PILOT versus TAU on the percentage of toxicology screens positive for primary substance of use.

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

7.4 Pilot Study Milestones

As a pilot study, this protocol is designed to inform a larger, multi-site randomized trial. All procedures employed in the pilot trial attempt to test those procedures intended for implementation in the subsequent larger trial [10].

As part of the pilot trial process [35], the study aims will be to identify, record, and correct for obstacles or “lessons learned” that may interfere with successful implementation of the larger randomized trial [10]. In keeping with this, four milestones have been identified to improve readiness to advance to a larger study, which has been informed by previous work employing similar milestones [14]. Additionally, the study will systematically track the obstacles encountered and lessons learned during implementation of this pilot trial to inform procedures for the larger trial.

Milestone 1: Convert the FORCE intervention to a manual-based PILOT intervention to enable replication at other sites. This milestone will be defined as successfully identifying and manualizing key components of the FORCE intervention into a PILOT manual. This will be accomplished through identification of key components and development of a preliminary intervention manual by the CTN 107 Team, including Rich Jones as the peer intervention expert. The key components and manual may be vetted by current FORCE Peers to ensure general fidelity to the current FORCE philosophy. During the training and implementation phase of the study, the study will also assess the ability to train personnel to implement the intervention with acceptable competence during the study.

Milestone 2: Identify critical site operational elements needed to successfully recruit for and conduct this trial in an ED setting and successfully replicate these critical elements in 3 sites. This Milestone will be addressed by determining critical site characteristics necessary for successful operationalization and implementation from the original FORCE program (e.g., adequate numbers of reported overdoses presenting to the ED, adequate identification of overdose survivors in the ED, adequate space in the ED for peers, peers having lived experience with substance use, naloxone education and distribution, etc.). Investigation of these elements will initially occur during site selection (which will define baseline TAU) and will be implemented by

identifying 3 sites that have or are able to implement 75% of critical PILOT site elements. Anticipated and actual recruitment will be monitored to inform whether the presence of critical site elements leads to successful recruitment. In addition, any changes in the presence or availability of these critical site elements, including any changes in TAU during the study period, will be measured quarterly to assess for sustainability of the critical elements and natural evolution of TAU.

Milestone 3: Investigate surrogate/composite markers of overdose to estimate sample size for a larger trial powered for mortality outcomes. The current pilot study proposes measuring repeat NFOOs and mortality by collecting information on self-reported NFOOs, fatal overdoses as reported by locator information (**Section 11.3.5**), and the National Center for Health Statistics' National Death Index, the latter of which will be examined after the study ends, as it takes greater than one year for the data to be available in this database **(Section 11.6**). The study will also evaluate initiation of MOUD as part of the secondary outcome (SUD Cascade of Care), as utilizing MOUD is known to be associated with decreased mortality for those with OUD (surrogate outcome). Lastly, the study will measure overdose risk behaviors known to be associated with repeat overdose and death (e.g., fentanyl use, intravenous drug use). Changes in each of these surrogate markers will be evaluated to determine which markers, or which composite of these markers, will best predict mortality.

Milestone 4: Determine the preliminary effectiveness of PILOT on reducing overdose risk behaviors (surrogate overdose marker). The study predicts that there will be a greater reduction in overdose risk behaviors in the PILOT group as compared with TAU. It would follow that a decrease in behaviors known to be associated with overdose risk would lead to a decrease in subsequent repeat overdose, a more distal outcome to be fully powered in the larger study. This Milestone will be defined as detecting a 10% lower rate of overdose risk behaviors in PILOT participants (any subgroup) as compared to TAU.

7.5 Study Timeline

After receiving CCTN and PRB approval of the protocol, approximately 6-8 months of trial preparation activities will elapse prior to commencing study enrollment. Trial preparation will include obtaining IRB approval (single IRB proposed), developing the data collection systems, developing the manual of operating procedures, developing the intervention manual, conducting all staff training, endorsing sites. Sites will be launched in a single wave if possible. Recruitment is expected to take approximately 12 months (approximately 4.2 participants enrolled per month per site; approximately N=150), with follow-up continuing for 7 months post completion of the recruitment phase. Approximately six months will be allowed for data cleaning and data lock after the end of the follow-up period. Therefore, data lock is projected to occur at approximately 27 months after PRB approval of the protocol.

8.0 STUDY POPULATION

A total of approximately 150 eligible individuals in the ED who have been identified as having experienced a NFOO in the past 30 days will be randomized (approximately 50 per each of 3 sites). Study staff will confirm self-reported overdose with the participant, 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. Randomized participants will be stratified by study site and homelessness status.

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. Alternative definitions for an overdose were considered; however, it was decided that this definition will appropriately identify the desired population for inclusion. In addition, the definition is consistent with current practice to identify OD survivors. Patients may be in the ED for an overdose event or for another SUD-related event if the NFOO occurred in the past 30 days.

8.1 Participant Inclusion Criteria

Individuals must meet all the inclusion criteria and none of the exclusion criteria to be eligible to participate in the study.

To be included in this study participants must:

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 non-fatal overdose involving opioids (NFOO) criteria:

   a. Having presented to the Emergency Department 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 Emergency Department within the past 48 hours for any SUD-related health issue, 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 2 out of 3 of the following: (a) signing appropriate releases to 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).

8.2 Participant Exclusion Criteria

Exclusion criteria include those who are:

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 [defined as two contacts] or unavailable for follow-up assessments).

8.3 Rationale for Inclusion/Exclusion

Including those without known SUD or primary SUD other than OUD: Although the most common SUD diagnoses in those with NFOO is OUD [11, 12] and a diagnosis of OUD is a stronger risk factor for repeat overdose than having other SUDs or no SUD, the following is the rationale for including those with no currently identified SUD or other primary SUDs: (1) the prevalence of SUD diagnosis in an overdose population presenting to the ED is not well described; (2) NFOO survivors without SUD/OUD do have increased risk of repeat OD; (3) NFOO survivors with no identified SUD or SUDs other than OUD may still/particularly benefit from a peer-based intervention addressing overdose risk reduction; and (4) individuals, particularly those on prescription opioids, may not initially acknowledge criteria for SUD, but later do so. For the purposes of this pilot study, those with no identified SUD or primary SUD other than OUD will be included, and since it has been shown that NFOO survivors without SUD/OUD are less likely to engage with outreach efforts [11], the primary outcome measure, screening and PILOT intervention have been tailored to include risk reduction for individuals in any SUD category. Secondarily, several steps on the SUD Cascade of Care can be achieved by those without SUD or for those whom MOUD is not indicated/desired, which will also be measured.

Excluding active suicidality and intentional/suicidal overdose attempts at screening: Because most overdose deaths involving opioids are accidental [36], and because managing an individual immediately after an intentional overdose is outside the scope of standard peer support service practices, individuals reporting that the Index NFOO was intentional, as well as those who are actively suicidal, will be excluded. Any participant who scores >0 ("not at all") on question 9 of the Patient Health Questionnaire-9 (PHQ-9; "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?") will have their suicidal ideation assessed by a medical clinician. Those with active suicidal ideation will be managed by the Emergency Department per standard care but will not be enrolled in the study. Those with "passive" suicidal ideation, defined as hopelessness and/or passive wish for or indifference about death, without current suicide plan or intention, will be eligible, as these symptoms are relatively common in those with active SUD.

Including those admitted to the hospital from the Emergency Department: Those admitted to the hospital from the ED but otherwise able to complete study procedures will be included (if able to meet other inclusion criteria), as it is the current practice of FORCE CPSSs to follow participants during hospitalization and after hospital discharge.

Including those discharged from the ED before screening can be completed: Some individuals may be identified as potential candidates for the study, but either leave Against Medical Advice (AMA) or are discharged from the ED before screening can be completed. If study staff are able, with verbal consent, to contact identified individuals with a NFOO within 72 hours of ED discharge, they can be screened for entry into the study and can be enrolled within one week of the ED discharge.

8.4 Strategies for Recruitment and Retention

Participants will be recruited from the ED at the time of ED admission (primary method of recruitment). Recruitment, approaching patients, screening, consent, and study procedures can be completed in-person or remotely, utilizing HIPAA-compliant videoconferencing and approved tele-consenting platforms as applicable. There will be two sources of referral: (1) During routine clinical care, patients presenting with or identified or suspected of having experienced an overdose in the past 72 hours, as identified by ED staff, including medical providers and TAU peers, can be referred for study screening; and (2) Research study staff will follow ED trackboards, coordinate with TAU peers and ED staff to screen for and identify individuals who may have experienced an overdose in the past 72 hours, and screen all SUD admissions for overdose in the past 30 days. This screening may include any individuals presenting with overdose or those who present with other substance use-related issues, including but not limited to, withdrawal, polysubstance use and consequences therein, and injection-related infection. The identification of an ED champion at each site will aid in successful recruitment and troubleshooting procedural or workflow issues with ED staff and providers. The study, including all study sites, will operate under the MUSC policies and procedures for recruitment given the SmartIRB master reliance agreement. As such, recruitment procedures will be the same across study sites, with any differences outside of the MUSC policies being specifically stated and approved as part of local study site standard operating procedures (SOPs).

8.4.1 Recruitment provisions for modified operations due to COVID-19, other population-level safety concerns, or low enrollment at sites:

8.4.1.1 Remote Recruitment/Enrollment

If restrictions to in-person patient care occur due to infectious diseases, such as COVID-19, or if ED patient flow slows due to other population-level safety concerns, potential research participants will be able to be identified and recruited in the ED utilizing remote techniques, including HIPAA-secure videoconferencing and/or approved tele-consenting via REDCap. All study procedures would be the same except the method of communication. For remote procedures, participating EDs will be provided with an electronic device (such as a "smartphone" or iPad) sufficient for HIPAA-compliant research consenting and procedures.

Additionally, if potential participants are identified within the ED, but unable to be reached remotely in the ED, research staff, with verbal consent, can follow-up with the participant after ED discharge, if the individual can be contacted within 72 hours of ED discharge; which mirrors the in-person contact allowance.

The method of recruitment and enrollment (in-person, remote, or both) will be tracked for each participant and summarized for scheduled DSMB meetings.

The remainder of the study outside of recruitment is designed for remote study completion. Regular in-services and/or educational briefings will be provided to ED staff to familiarize them with the study eligibility criteria.

It will take sites approximately 12 months to enroll the proposed sample into this study. The average weekly randomization rate across all three sites is expected to be 1-2 participants/week/site (4.25 per month proposed for each site).

8.4.1.2 Community Recruitment

If site recruitment goals in the ED are below-goal for two or more consecutive months, after discussion with the Lead Team, a site may be able to commence recruitment efforts in the community (e.g., recruit and enroll participants outside of the ED setting), with all screening/enrollment/study procedures completed remotely. This will only be pursued in the case of modified operations or restrictions in the hospital or ED and/or a failure to identify NFOO survivors to engage regarding study enrollment. The method of recruitment and enrollment (ED or community) will be tracked for each participant and summarized for scheduled DSMB meetings. The following will be the modified Inclusion/Exclusion Criteria for Community Recruitment:

8.4.1.3 Modified Inclusion/Exclusion Criteria for Community Recruitment

<u>To be included in this study, participants recruited from the community must</u>:

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

2. Self-report having a known or suspected overdose involving opioids in the past 30 days that involved transport or admission to an ED.

3. Be able to provide sufficient locator information, defined as identifying at least two 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 2 out of 3 of the following: (a) signing appropriate releases to 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).

Exclusion criteria for those recruited from the community include those who are:

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 [defined as two contacts] or unavailable for the follow-up assessments).

Participants recruited from the community who are randomized to TAU will receive, from the research study staff, a referral to treatment, consisting of a handout providing names, locations, and telephone numbers of addiction treatment services and naloxone resources in the area and telephone access to call a clinician or facility of their choice, which will be informed by their method of healthcare coverage. Addiction services can include a range of treatments with varying intensity and duration, based on local resources and patient preference.

Community-recruited participants randomized to PILOT will commence the PILOT intervention remotely or in-person with the on-call PILOT peer, according to the PILOT intervention manual.

9.0 SITE SELECTION

9.1 Number of Sites

In this pilot study, participants will be recruited from three sites in the US over a 12-month period. The study period will be seven months (6-month intervention period and 1-month follow-up assessment at Day 210).

9.2 Site Characteristics

Three sites that already have established and funded Peer Recovery Services in their ED (TAU) will participate in the study. Sites will be screened for willingness to deliver PILOT, willingness to randomize patients in PILOT vs. TAU, and current numbers of patient who are admitted to the ED with an identifiable overdose per month.

Participating sites should:

1. Have sufficient numbers of ED admissions with an identifiable overdose to randomize 1-2 participants per week during study enrollment (4.2 per month proposed for each site).
2. Currently provide peer support services in the ED for overdose survivors or those with an SUD that do *not* regularly follow participants into the community (preferably a single point of contact in the ED and resources provided).
3. Provide adequate space in the ED or in a nearby location to accommodate research staff and execution of the study protocol.
4. Be able to provide after-hours clinical backup for study-related emergencies.
5. Be willing to deliver the manualized PILOT intervention.
6. Have the ability to provide naloxone kits and/or information on obtaining naloxone to patients per state regulations.
7. Meet 75% of critical site characteristics as determined by Milestone 2.
8. Have an ED champion as part of current staff that will assist with integration of study staff and PILOT peers into the ED workflow and assist with issues of recruitment, processes, or engagement by ED staff.

9.3 Rationale for Site Selection

Sites that already have ED peer recovery services in place will be utilized because the successful operationalization of a peer recovery intervention in an ED setting is a separate endeavor outside the scope of this pilot study (which will evaluate the effectiveness of a specialized overdose peer who engages with participants in the ED AND follows participants into the community). To evaluate the effectiveness of the PILOT intervention (which is a separate question from how to effectively operationalize a successful peer team in an ED setting), the study will start with the premise that peer support services have already been successfully operationalized and are functional to serve as a comparator group.

To optimize fidelity of the intervention, all 3 sites will be willing to adhere to the PILOT manual if there are divergent peer recovery approaches.

Because MOUD receipt strongly predicts treatment retention, all 3 sites will have to either offer MOUD in the ED setting or not offer MOUD in the ED setting, and all 3 sites will need to have a community system in place to provide MOUD for individuals who do not have insurance.

10.0 STUDY PROCEDURES

10.1 Screening

Patients will be recruited at each ED site, either in-person or via remote techniques (if needed). Study sites will operate under the MUSC policies and procedures for recruitment given the SmartIRB master reliance agreement. As such, recruitment procedures will be the same across study sites, with any differences outside of the MUSC policies being specifically stated and approved as part of local study site standard operating procedures (SOPs). Research staff will work during times to include evenings and weekends to ensure success with enrollment. Research staff will identify patients seen in the ED by screening, reviewing the EHR trackboards and by provider or TAU peer referral. Research staff will keep a log of all patients approached and the outcome of that approach (Screening and Approach Log). Potential participants identified will be evaluated by a member of the research staff for eligibility.

Patients will be stabilized per ED usual care and receive TAU per that ED site, noting that each site will have an operationalized peer support specialist system already in place in the ED which may be a part of TAU (**Figure 1**). After clinical stabilization and TAU, research staff will ask for verbal consent to complete screening forms and assessments, which will include questions about overdoses in the past 30 days, reason for the ED visit, and other items that may exclude that individual from study inclusion. Research staff will follow an approved verbal consent script which details how their information might be used/exceptions to confidentiality based on urgent medical concerns during the screening process.

Patients who appear to be eligible will then be asked about interest in the study. If the answer is yes, research staff will describe the study and if the participant remains interested and would like to continue, written informed consent will begin.

Those who are not eligible for the study following screening questions or who decline will continue with TAU in the ED (including additional interaction with a TAU peer from the hospital, as applicable; all participants in the least will receive a referral list of options for follow-up care, access to a telephone, and information about obtaining naloxone). 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). A waiver of signed consent will be acquired from the Medical University of South Carolina (MUSC) Institutional Review Board (IRB) to administer this brief survey for reasons for study refusal and to maintain and use patient characteristic data. Those who complete the Screening Exit Survey will be compensated $15. Identifying information will be collected to compensate participants but will not be linked with their survey responses. This information may be used to better inform recruitment strategies, evaluate feasibility of the peer intervention program in the ED from a participant-interest standpoint, and be used to contrast characteristics of consenting and non-consenting individuals.

10.2 Eligibility Confirmation and Enrollment

After the Screening Enrollment Form has been completed and the patient meets basic eligibility criteria, they will be asked to give written informed consent.

10.2.1 Informed Consent Procedures for Participants

The MUSC IRB will be used as the IRB of record for the study, and the study will comply with all necessary requirements at each site. Each site will use the IRB-approved Informed Consent.

The informed consent procedures will be flexible to accommodate the needs of patients admitted to the ED. Candidates for study participation will be provided a copy of the current IRB-approved consent form for review. An appropriately qualified and trained individual will explain the study procedures and the potential risks and benefits of participating in the trial, as well as answer all the candidate's questions about the study. Staff will be available to answer questions about the consent form while participants are reviewing it. Participants will be asked to explain the study in their own words (consent teach-back form) to research staff. This will not be exclusionary but will aid in determining that consent is informed and understood.

Because of the time constraints of completing the assessment and initial intervention in the ED, the informed consent form will be as brief as possible within the constraints of adequate human subjects' protections. These documents will include a description of the following key elements: general study procedures; the follow-up interviews; risks and benefits of the PILOT intervention and study procedures; alternatives to participation in the study; confidentiality; compensation for participation; a statement that participation is voluntary and that they may freely withdraw participation at any time; and information about whom to contact with questions or in case of emergency. The Informed Consent includes assurances of confidentiality (including a Certificate of Confidentiality), as well as exceptions to confidentiality, and that the decision to participate will in no way influence other aspects of the patient's treatment.

If recruitment and study procedures are being completed remotely, REDCap electronic consent (e-consent), combined with a HIPAA-secure video conferencing platform, will be used during the consent process (preferred). Participants are also able to view the informed consent document on a computer or phone via REDCap and complete a phone call with research staff. Video chat functionality will only be used if all parties have the availability and is not required for consent to be performed. Each study site will have their own MUSC REDCap database managed by the lead research team. Using these systems, signatures on the consent form may be obtained electronically via REDCap.

Participants will also be asked for locator information for self, relatives, or friends to enable the study staff to find them during the 6-month intervention portion of the trial as well as at the 210-day follow-up visit. This information will be reviewed with participants during each study visit and more frequently, as needed, and updates will be made to the information as necessary.

Given the multi-site nature of the trial, it is possible that ancillary studies will be proposed before or after the study begins recruitment. For this reason, during the informed consent process, the study will seek permission to contact the participant in the future about other study opportunities.

10.2.2 HIPAA Authorization, 42 CFR Part 2, and Medical Record Release Forms

Each site will utilize a Research Authorization, HIPAA disclosure form and/or 42 CFR Part 2 allowing study access to confirm engagement in SUD treatment, as required by their institutions. Sites will be responsible for communicating with their IRBs or Privacy Boards and obtaining the appropriate approvals or waivers to be in regulatory compliance with local requirements.

10.3 Eligibility Confirmation, Screening, and Baseline Assessments

After screening eligibility is confirmed, the patient will be entered into the data system to complete inclusion/exclusion information, and to confirm eligibility. The enrollment procedures will be captured through a centralized process managed by the CTN Data and Statistics Center (DSC). Study patients who do not complete all screening assessments or who are otherwise found to be ineligible for participation in the study will be considered screen failures.

The site's research team will review screening assessments to determine final eligibility for randomization. In most instances screening and baseline assessments may be performed during the same visit, and randomization will occur at that same visit (typically).

10.4 Randomization

Eligible participants will be randomized in a 1:1 ratio to PILOT or TAU after confirmation of study eligibility status per the study protocol. Randomization will be stratified by study site and homelessness status (yes/no). The randomization process will be conducted in a centralized process through the DSC. A permuted block randomization procedure with random block sizes will be implemented to balance per site and homelessness status, and randomization details such as block size will not be conveyed to staff or participants. The DSC statistician will generate the randomization schedule using balanced blocks of varying sizes within strata to ensure lack of predictability along with relative equality of assignment across treatment groups. The block size also will be randomized to prevent the potential for study personnel guessing the next assignment which sometimes happens with a fixed block-size.

Randomization will be performed by a designated study staff member over the internet using the Enrollment Module in Advantage eClinical. The 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 patient due to the intent-to-treat nature of the study.

10.5 Treatment/Intervention

In this study, participants will be randomized to PILOT or TAU. Medical care and management of the overdose or medical issue will be treated the same across both groups and will not be impacted by group assignment.

Baseline assessments will be collected through participant interviews and a toxicology screen. Management of OUD, if present, will be managed based on standard of care in the hospital and will follow local practice. A TAU peer system will be operational in each ED site and will interact

with participants across both groups in an SBIRT-like model as indicated and available at that site.

TAU: For the purposes of this study, TAU is defined as usual medical treatment, including MOUD if indicated/available and any TAU peer support services as offered per standard practice at the site ED. Research staff will administer baseline assessments and toxicology screen during the ED Index visit and arrange for 30-. 90, and 180-day study visits to occur via phone and/or community visit and/or video chat. Participants randomized to TAU will continue receiving local standard of care through time of ED discharge/transfer.

PILOT: After randomization has occurred, for individuals randomized to PILOT, a PILOT peer will be contacted to travel to the ED to meet with the participant or a phone call/video chat will be organized. Participants randomized to PILOT will also continue local standard of care (TAU), as well as the PILOT intervention. This may mean that PILOT participants will interact with both a TAU peer and a PILOT peer and a recommended collaboration process will be formalized with each site based on site characteristics.

The PILOT intervention will be delivered according to the PILOT intervention manual over the 6-month treatment period. PILOT will begin after study randomization and the PILOT peer will meet the participant and arrange for follow-up visits per the PILOT protocol. The PILOT peer will be provided with locator information as collected by research staff. Research staff will administer baseline assessments and toxicology screen during the Index visit and arrange for 30-, 90-, and 180-day study visits to occur via phone and/or community visit and/or video chat.

The research staff will also record key clinical elements provided during ED visit (e.g., MOUD applicable/offered [via study CRF], TAU peer meeting, and resources provided [captured on the study visit checklist]).

10.6 30-, 90-, and 180-day Assessments

Study assessments during the study intervention phase are expected to be conducted at 30-, 90-, and 180-days post randomization. The day of randomization will be considered study Day 0. Follow-up visits may be completed in person at the site or via telephone, video chat, and/or electronic communication by study staff. Additionally, research staff will have the option to meet participants at a convenient location in the community to collect study assessments and data, if necessary. Research staff safety protocols for community visits will be implemented for research study visits (detailed in the study MOP and local site SOPs) and can include the following: at least 2 staff members attending the visit at all times; providing location information for the study visit; checking in immediately with supervisors before and after visits have occurred; and prioritizing meetings in public spaces.

Reminders regarding study visits will be given to the participant several times leading up to their next study visits (using email, phone call, or text based on the preference of the participant). In addition, research staff will send a reminder in the mail/text/email/phone or social media (based on study participant preferences documented on the locator information form) approximately seven days before the scheduled follow-up visit, with an additional reminder notification via

mail/text/email/phone/social media (based on study participant preference) the day before the scheduled follow-up visit.

Study visits will entail collection of self-report data, questionnaires, interview questions, and oral fluid toxicology testing. Self-report, questionnaire, and interview data will center on substance use, engagement with recovery and/or formal SUD treatment, including medications, and overdoses during the interim period. Appropriate release of information will be obtained to confirm treatment engagement if needed. These assessments are listed in **Section 11** and their flow is operationalized in the study MOP.

If a participant is unable to utilize a phone for any reason during any study assessments, research staff will utilize locator information to arrange to meet the participant in the community, according to MOP criteria, to administer study assessments and toxicology sample collection.

10.7 Weekly Mobile Surveys

To augment data collection in this trial, remote surveys will be administered to participants on their mobile devices using the Research electronic data capture (REDCap) system [37], which is available to MUSC investigators and external affiliates (i.e., all site research staff). REDCap is a HIPAA-compliant, cloud-based, commercial off the shelf data management system that can be used for creating and distributing surveys. Remote surveys will be administered to participants following randomization and will not occur on weeks when study visits are scheduled (Days 30, 90, 180, and 210). Given that only four study visits are scheduled during this trial, data collection between visits is critical for capturing a more accurate picture of harm reduction, the recovery process, and steps taken in the cascade of care.

Remote surveys on REDCap will be delivered to the participant's mobile phone as a survey invite link through an SMS text message. Surveys will be administered weekly. The survey invite includes an individualized link that contains embedded data, at individually calibrated time points. If the participant does not have a smartphone (anticipated to be <10% of participants), they will be able to borrow one during the study. Responses will be date and time-stamped and participants will receive compensation for completing each remote survey.

10.8 Follow-Up Assessment (Day 210)

Participants will be followed for 210 days (7 months) after randomization (180 days/6 months of Intervention, and a one-month/Day 210 post-intervention follow-up). Assertive outreach procedures will be implemented to locate and assess participants at the follow-up time point and to minimize missing data. These procedures are detailed in the study MOP. Arrangements for ongoing treatment following the study will occur as per local practice. There will be flexibility in exact timing of the intervention assessments to accommodate participants' schedules and to allow for either in-person or electronic communication (e.g., phone, video chat, community visit, etc.).

10.9 Premature Withdrawal of Participants

All participants will be followed for the duration of their 210-day (7-month) participation in the study unless they withdraw consent, die, or the investigator or sponsor decides to discontinue their enrollment for any reason. Reasons for the investigator or sponsor terminating a participant from

the study may include, but are not limited to, the participant becoming a threat to others, lack of funding, or DSMB early termination of the study for safety or effectiveness reasons.

Premature withdrawal may occur should a participant refuse the intervention to which they were randomized. To minimize loss to follow-up, efforts to pursue participant locator information such as multiple contact options (e.g., phone, address, email, social media) and collateral contact information will be maintained. At any time, participants may decide that they no longer wish to continue to participate in the study.

10.10 Study Halting Rules

This study entails a single point of intervention, randomization to PILOT or TAU. The use of Peer Support Services in assisting those with SUD is a low-risk intervention that is clinically well-established [13-15, 17]. The study does not anticipate any circumstances that would necessitate halting the study based on safety or efficacy. There are no plans to conduct an interim efficacy analysis or sample size re-estimation as part of this trial. Nevertheless, the study DSMB or the study sponsor may choose to halt the study should they identify issues related to study conduct, funding, or regulatory environment. Should this occur, the lead investigator will work with the IRB of record and each of the local sites to promptly inform them of the reasons for study termination or temporary suspension and to identify the circumstances in which the study may resume.

10.11 Blinding

No blinding will be used for the interventions in the PILOT study. The lead team will ensure that all research staff, peers, and any affiliated staff have proper training on minimizing bias in unblinded trials. The next randomization assignment will not be known to research staff, peers, or ED staff. The assigned group will not be known until all screening data have been entered into the study database and the randomization assignment is generated and provided to the research staff. Research staff will not be able to predict the next randomization spot given that the other study sites will affect randomization ordering. This will help to minimize bias among study staff.

10.12 Participant Reimbursement

Because of the expected difficulty of maintaining high follow-up rates in the study population, adequate compensation for time and inconvenience is critical. Compensation will be in accordance with the IRB of record's policies and procedures, subject to IRB approval, and will occur on the following schedule, and allowances can be made for pro-rated compensation for study sessions that are interrupted or completed on different days:

- Consent and baseline data collection
- 30-day assessment
- 90-day assessment
- 180-day assessment
- Follow-up assessment (Day 210)
- Remote assessment compensation: 24 surveys administered

Individuals who screen out or decline study entry will have an option to complete a brief survey to evaluate reasons for study decline or screen-out and will be compensated according to the MOP. Compensation will occur following each visit with procedures and payment practices specified in the MOP and local site SOPs.

11.0 STUDY ASSESSMENTS

11.1 Overview

All assessments for this study are brief, balancing the value of comprehensive data against feasibility and to minimize assessment reactivity that can obscure treatment effects [38]. The practical issue is that extensive study assessments are likely to interfere with the rapid pace of clinical treatment in the ED setting. A cumbersome assessment process is also likely to impede the successful completion of the study through an adverse impact on recruitment and would not be part of real-world clinical practice. Excluding collection of study participant characteristics and locator information, the patient baseline data will include a brief instrument assessing overdose events, past 7-day alcohol and drug use including opioids using the Timeline Follow Back (TLFB) method, use of other substances, and overdose risk factors. The Table of Assessments (shown below) provides a summary of study assessments. The expected time burden for the screening and baseline assessments is around 2-3 hours, not including consent procedures and toxicology. Some assessments will be administered after randomization assignment while the participant may be waiting in the ED for the PILOT peer to arrive or to be discharged. Assessments collected at 30, 90, 180, 210 days post randomization will be similar in content and will be kept brief.

11.2 Table 1: Table of Assessments/Forms

Assessment	Time Needed to Complete *(only for ppt assessments)*	**Screening**	**Random-ization**	**Baseline**	**Day 30**	**Day 90**	**Day 180**	**Day 210**	**As Needed**
		(Index ED Visit/Enrollment) – Virtual or In-person			**Phone, Virtual, or In-person**	**Phone, Virtual, or In-person**	**Phone, Virtual, or In-person**	**Phone, Virtual, or In-person**	
Screening									
Screening Enrollment Form	5 mins	X							
Prisoner Status Assessment	2 mins	X							
Demographics	5 min	X							
Patient Health Questionnaire-9	2 mins	X			X	X	X	X	
Screening Exit Survey	10 mins	X							
Written Informed Consent	30-45 mins	X							
Inclusion/Randomization and Study Visits									
Study Enrollment Form			X						
Visit Documentation				X	X	X	X	X	
Locator Information Form	5-10 mins			X	[X]	[X]	[X]		[X]
Overdose Information	3 mins			X	X	X	X	X	
Urine Drug Test	5 mins			X	X	X	X	X	
Overdose Risk Behavior Checklist	3 mins			X	X	X	X	X	
Harm Reduction Checklist	3 mins			X	X	X	X	X	
Step 2-7 Assessment Form (SAF 2-7)	4 mins			X	X	X	X	X	

Assessment	Time Needed to Complete *(only for ppt assessments)*	Screening	Random-ization	Baseline	Day 30	Day 90	Day 180	Day 210	As Needed
		(Index ED Visit/Enrollment) – Virtual or In-person			Phone, Virtual, or In-person	Phone, Virtual, or In-person	Phone, Virtual, or In-person	Phone, Virtual, or In-person	
MOUD Confirmation Assessment (*confirmed via objective measures)*	3 mins				X	X	X	X	
MOUD Current Status	2 mins			X	X	X	X	X	
Readiness Ruler	1 min			X	X	X	X	X	
Alcohol and Substance Use History (PhenX Tier 1)	10 mins			X					
Timeline Follow-Back (7 day)	3 mins			X	X	X	X	X	
DSM-5 Checklist	5-10 mins			X	X	X	X	X	
ED MOUD Administration *(obtained from EMR)*				X					
End of Treatment							X		X
Assessment of Recovery Capital	8 mins			X	X	X	X	X	
Chronic Pain History	1 min			X					
Tobacco Use History	2 mins			X					
Fagerstrom Test for Nicotine Dependence	2 mins			X					
Cannabis Use Assessment	1 min			X			X	X	
Quality of Life	3 mins			X	X	X	X	X	
Crime and Criminal Justice	3 mins			X	X	X	X	X	
Treatment Satisfaction Form	5 mins							X	X
Administration or Non-Visit Based Forms									
Mental Health Follow-up Assessment	2 mins								X
ED Visits and Hospitalizations	5 mins								X
Screening Approach	1 min								X
Contact Log	5 mins								X
Death Form	5 mins								X
Protocol Deviation and Review Forms	5 mins								X
Study Completion Form	2 mins							X	X
Inventory – Supplies Form	5 mins								X
TAU Characterization Form	15-20 mins								X
Peer Characterization Survey	5-10 mins								X
Remote Assessments									
Mobile Weekly Surveys	3-5 mins				X[b]	X[b]	X[b]	X[b]	
PILOT Intervention									
PILOT Intervention Activities Log	1-5 mins			X	X	X	X	X	
Supervisor Log	3-5 mins							X	
Rolling Progress Note	2-10 mins							X	

Notes: [b]=administered weekly

[X]= assessment is reviewed and updated as needed

11.3 Screening Measures

11.3.1 Screening Enrollment

Individuals will meet with a member of the research staff to be evaluated for study eligibility. This assessment will be conducted after verbal consent, and before enrollment into the study. It will include questions about overdose involving opioids, age, reason for ED visit, and other questions that may exclude an individual from the study. If the individual had an overdose in the past 30 days, the Screening Enrollment Form asks whether the overdose was accidental or intentional. If the individual's answer is "intentional", the individual will be excluded from study participation, but the response will also prompt study staff to have the individual evaluated by the study clinician for active suicidal ideation and trigger completion of the Mental Health Follow-Up Assessment Form.

The Screen Enrollment form also documents eligibility during the screening phase, before written informed consent is obtained. Eligibility will be re-assessed prior to randomization, and then continually as appropriate. Only participants who continue to meet study eligibility criteria will be allowed to continue with the screening process and randomization.

11.3.2 Prisoner Status Assessment

Individuals approached in the ED will complete a Prisoner Status Assessment to determine that they do *not* meet the OHRP definition of prisoner. If they do meet the definition, they will not be able to enter the study, but will continue to receive TAU as established in the ED. The individual is not assigned a number and no data is retained from the encounter. If the individual does *not* meet the definition of prisoner, they will be invited to learn more about the study and complete the informed consent process.

11.3.3 Demographics Form

The PhenX Demographics form collects information about demographic characteristics of the participant, including sex, date of birth, ethnicity, race, education, employment status, and marital status. A study-specific demographics form collects information about homelessness, criminal justice supervision, employment, insurance status, living arrangements, etc.

11.3.4 Alcohol and Substance Use History (PhenX Tier 1)

The Substance Abuse and Addiction Collection of the PhenX Toolkit (http://www.phenxtoolkit.org/) includes measures that are being adopted across NIDA-funded research. The Core Tier 1 collection includes measures for substance use history, such as age of onset, lifetime use for alcohol, tobacco, and other substances. The most up to date version of the PhenX questions will be used (Version 20, dated December 2019).

This form will be administered at baseline only and will assess lifetime and past 30 day use of alcohol, non-medical use of prescribed controlled substances, non-prescribed pharmaceutical prescription drugs and illicit drug use. It will also assess, as applicable, age of first use. For the baseline assessment, this form will be administered contiguous with the 7-day TLFB to avoid repeat assessment of drug use.

11.3.5 Informed Consent and Research Authorization

Participants will review and sign the IRB-approved consent form and any other related documents (e.g., Research Authorization, HIPAA authorization) in accordance with IRB requirements either in person or electronically through REDCap eConsent. Procedures for obtaining informed consent and related authorizations are detailed in **Sections 10.1 and 10.2**. Only patients who continue to meet study eligibility criteria will be allowed to continue to the enrollment phase.

11.3.6 Participant Eligibility Summary and Randomization

The Patient Eligibility Summary and Randomization form collects information regarding eligibility Only participants who continue to meet study eligibility criteria will be allowed to continue with randomization.

11.3.7 Screening Exit Survey

Patients who do not pass the screening instrument and/or are not interested in participating in the study will have the option to complete a brief, de-identified, interviewer-administered survey asking about reasons for ED visit, demographics, substance use history, overdose history, Narcan availability, and reasons for study decline (as applicable). Compensation will be provided for completing this survey, but as the survey will not be associated with identifying information, it will be completed with an approved waiver of written consent.

11.4 General Measures

11.4.1 Patient Health Questionnaire (PHQ-9)

The Patient Health Questionnaire (PHQ-9) [39] will be used to assess depressive symptoms, including suicidal ideation. If the participant responds to “Thoughts that you would be better off dead, or of hurting yourself in some way” with any response other than “Not at all”, it will trigger a requirement to provide the participant with Suicide Hotline information and other mental health resource information per the MOP. When the response is recorded at screening/baseline, the study clinician, or in cases where the study clinician is not reasonably available, an available non-study clinician at the site will be notified. All sites should monitor participant responses to this PHQ-9 question, as well as participant spontaneous expression of potential suicidal/homicidal ideation and have procedures in place to ensure patient safety. In all cases, participant mental health follow-up should occur according to site-specific SOPs. For any endorsement of potential suicidal ideation reported on the PHQ-9, completion of the Mental Health Follow-up Assessment form will be required.

11.4.2 Visit Documentation

This form documents visit attendance, non-visit attendance, and missed visits. This form additionally captures whether any ED visits or hospitalizations occurred since the last study visit, and if so, it triggers the ED Visit and Hospitalization form. This assessment has been recently developed to document visits that could occur out of window, off site, or missed due to COVID-19. This is a visit-based form expected at all visits that would typically have a regular missed visit form. If a visit is missed for any reason, this form will capture the reason a study visit was missed. Completing this form and indicating that the visit was not attended will remove the requirement

for all assessments scheduled for that visit. Active tracking and follow-up should be performed for all missed visits. The form also captures specific data collection settings if applicable (such as in clinic, off-site, remote, or in a controlled environment).

11.4.3 Locator Information Form

A locator form is used to obtain information to assist in finding participants during treatment and at 30-, 90-, and 180-day phone assessments as well as a 210-day follow-up assessment. This form collects the participant's current address, email address, and phone numbers (updated frequently or as needed) as well as information such as social security number, driver's license number and other information to aid in searches of public records. To facilitate locating participants and keeping up-to-date phone numbers if direct contact efforts are unsuccessful, addresses and phone numbers of family/friends or other contacts who may know how to reach the participant are collected (minimum of two required to be eligible for the study). This information will be collected at after obtaining informed consent and will be updated at each visit or whenever the participant reports a change in locator information. No information from this form is used in data analyses. At screening/baseline, at least two contacts must be identified.

11.4.4 MOUD Current Status

This form will be used to assess current MOUD use, and if affirmative, MOUD formulation, dose, and date of last dose.

11.4.5 Timeline Follow-Back (TLFB)

The Timeline Follow-Back [40] procedure will be used to elicit the participant's self-reported frequency of use and route of administration of nicotine, opioids, marijuana, stimulants, benzodiazepines, sedatives, hallucinogens, inhalants, and alcohol for the past seven days. At enrollment, substance use will be reported by the participant in the 7-day period prior to informed consent. At the 30-, 90-, 180-, and 210-day follow-up visit, substance use is reported for 7 days prior to the visit date. This will be completed remotely or during in-person visits. These procedures will also be used to capture days of MOUD use (yes/no) during the entire study period.

11.4.6 DSM-5 Checklist for Substance Use

The DSM-5 Checklist is a semi-structured, interviewer-administered instrument that assesses for substance use in the past 12 months, and if affirmative, assesses for the presence of 11 symptoms of substance use disorders based on DSM-5 diagnostic criteria including: opioid, alcohol, amphetamine, cocaine, cannabis, and sedatives. If SUD is endorsed, participants will be asked about primary substance of use.

11.4.7 ED MOUD

This form will record information regarding medications for OUD administered during the index ED admission, according to patient self-report at the time of ED discharge, including medication name (methadone, SL buprenorphine, SL buprenorphine/naloxone, oral naltrexone, and extended-release naltrexone), date, and total dose administered (if known). This data will be used to determine MOUD exposure in the ED Index visit.

11.4.8 End of Treatment Form

This form tracks the participant's status regarding the study intervention. It will be completed at the end-of-treatment visit or at the 180-Day visit (for participants who complete study participation).

11.4.9 Quality of Life (Qol)

Quality of life will be measured using a standard form used in the CTN, the CDC Behavioral Risk Factor Surveillance System (BRFSS) HRQOL-4). This measures general health of the participant and healthy days out of the last month (physical and mental health).

11.4.10 Crime and Criminal Justice

This form captures data on incarceration, recent crimes, and recent contact with the law.

11.4.11 Treatment/Study Satisfaction Form

Participants will complete a Treatment/Study Satisfaction Form at the 210-Day visit. This form will assess the acceptability of study procedures, time, compensation, treatment intervention and other aspects of their experience.

11.4.12 ED Visits and Hospitalizations

Data will be collected on health care utilization (inpatient and outpatient) between the index and 30-, 90-, 180-, and 210-day assessments and on an as needed basis for spontaneous reporting that occurs between study visits. ED visits and hospitalizations will be collected through self-report and review of participant electronic medical records.

11.4.13 Chronic Pain History

This brief questionnaire evaluates the presence of self-reported chronic pain (6 months or longer) and average daily pain severity.

11.4.14 Study Completion Form

This form tracks the participant's status in the study. It is completed at the 210-Day visit, after the 210-Day follow-up visit window lapses for participants who do not complete this final follow-up, or after the site confirms that a participant is permanently done with the study (e.g., participant died or withdrew consent). This form is used in data analyses to address variables such as treatment retention and completion. This form also provides a location for the site PI attestation of review of all study data.

11.5 Measures of Primary and Secondary Outcomes

11.5.1 Overdose Risk Behavior Checklist (ORBC; Primary Outcome)

The Overdose Risk Behavior Checklist (ORBC) is an expanded and modified 13-item self-administered questionnaire that was adapted specifically for this pilot trial from similar questionnaires utilized in prior studies to capture overdose risk behaviors in this or similar populations [23, 24], and developed based on known factors associated with risk for overdose

[23, 28-33]. The questions measure the frequency at which individuals used drugs alone; used in a new place/environment; used other substances (alcohol, benzodiazepines, stimulants) within 2 hours of opioids; used more than one opioid; used more than the usual amount; and used inhaled or injected opioids. Some branching/sub questions exist, which are not counted in the total score or item number count. The total risk score (ranging from 0-44 based on 11 items) is an aggregation of responses to specific individual questions, with higher levels indicating a greater frequency and number of overdose risk behaviors. The overdose risk behavior questionnaire is administered at scheduled study visits.

11.5.2 Steps Achieved Along SUD Cascade of Care Assessment Battery (Secondary Outcome)

At 30, 90, 180, 210 days post enrollment, 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, Steps Achieved Assessment (Step 2-7 Assessment Form), MOUD Confirmation Assessment, DSM-5 Checklist for Substance Use, Urine Drug Test, and the Assessment of Recovery Capital (ARC) Scale.

11.5.3 Harm Reduction Checklist

The Harm Reduction Checklist was developed specifically for this pilot trial. This form compiles items assessing risk mitigation factors for opioid-related overdose. The HRC constitutes Step 1 of the secondary outcome (SUD Cascade of Care). Step 1 – Receipt of and Participation in Harm Reduction Services – includes items assessing a range of harm reduction services such as receipt of harm reduction psychoeducation, Narcan, fentanyl test strips, and treatment for comorbid health and mental health conditions. This form also assesses for prescribed opioid analgesic use, with formulation and dose, as applicable.

11.5.4 Step 2-7 Assessment Form

This form was developed specifically for the PILOT trial and will capture information on the participant's engagement in Steps 2-7 on the Cascade of Care (research staff administered). This form will assess engagement in care/treatment and frequency of attendance (Step 2 measures "any" care/treatment attendance; Step 3 measures "regular" care/treatment attendance), as well as initiation of MOUD (Step 4) and duration on MOUD (Steps 5-7; based on an assessment of frequency of MOUD use and confirmation per MOUD Confirmation Assessment). Although this form will be administered at baseline for descriptive purposes, it will only be used for the Steps Achieved Along SUD Cascade of Care Assessment Battery at 30-, 90-, 180-, and 210-days post enrollment, as applicable.

11.5.5 MOUD Confirmation Form

This form will be used to document confirmation of MOUD through toxicology screen, treatment provider or pharmacy confirmation, or via HIPAA-compliant photo or video chat confirmation of a MOUD medication bottle or prescription. This form will also be used to document any issues encountered with video capture of MOUD confirmation (poor connection, poor lighting, no sound, etc.). MOUD confirmation must be verified through objective means and cannot be self-reported by the participant.

11.5.6 Assessment of Recovery Capital (ARC) Scale [34]

This validated assessment quantifies addiction recovery strengths through 10 domains and captures the personal and environmental resources that are associated with recovery (known as recovery capital). Responses on this form will be used to inform progress on the Cascade of Care.

11.6 Exploratory Outcomes

11.6.1 Overdose Information [41]

At baseline, 30-, 90-, 180-, and 210-days post enrollment, participants will be asked about lifetime overdose experiences (baseline) or opioid-related overdose events since the time of the last study visit (30-, 90-, 180- and 210-day). This form will date, quantify, and describe overdose events experienced as well as general symptoms/outcomes of overdoses experienced (e.g., Was Narcan administered? Did the overdose result in ED visit or hospitalization?).

11.6.2 Death Form

Data will be collected on all-cause mortality, including fatal overdose, with information from persons listed on the participant's locator form when participants are lost to follow-up throughout the study. Attempts will be made to contact any participant who is lost to follow-up throughout their visit windows (until Day 210 follow-up visit).

11.6.3 National Death Index

Attempt will be made to account for all participants who may have died during the study or after the study ends, by querying the National Center for Health Statistics' (part of the Centers for Disease Control and Prevention) National Death Index. This is a list of all persons who have died in the U.S. Data. After the study has ended, identifiable information will be used, including name, date of birth, sex, social security number, state of residence to search this database for death and cause; specific consent for use of PHI after the study ends will be obtained from the participant during the informed consent. Records in the NDI database are delayed by 18-24 months, so the Lead Node will be responsible for NDI searchers after the study has ended.

11.7 Safety Data

11.7.1 Mental Health Follow-Up Assessment

During completion of the Screening Enrollment Form, individuals who have had an overdose in the past 30 days will be asked whether the index overdose was accidental or intentional. If the individual's answer is "intentional", the individual will be excluded from study participation, but the response will also prompt study staff to have the individual evaluated by the study clinician for active suicidal ideation and trigger completion of the Mental Health Follow-Up Assessment Form.

The PHQ-9 asks participants if they have had "thoughts that you would be better off dead, or of hurting yourself in some way" over the past two weeks. During screening in the ED, any response to the above question other than "Not at all" will prompt the research staff to notify the study clinician or, in cases where the study clinician is not reasonably available, a non-study clinician at the site (per verbal pre-screening script and Informed Consent). If subsequent clinician evaluation reveals that the patient has current, "active" suicidal ideation, then the patient will not be eligible

for the study. However, continued assessment and/or intervention for patient's suicidality will still be conducted in accordance with TAU in that ED and with site-specific SOPs. The treating ED staff should be made aware of the individual's suicidality if not already known, and this will be discussed in both the verbal screening script and Informed Consent.

After enrollment in the study and during subsequent study visits (conducted remotely or offsite within the community), participant endorsement of potential suicidal ideation either on the PHQ-9 or spontaneously will trigger a requirement to provide the participant with national or local mental health resource referral/contact information (e.g., suicide hotline information) per the MOP.

In all cases, endorsement of possible suicidal ideation on the Screening Enrollment Form and PHQ-9 will trigger a requirement for completion of an MHA Mental Health Follow-Up Assessment form. A protocol deviation is required if this form is not completed, or the above procedures are not followed. Note: the Mental Health Follow-Up Assessment form is *not* completed when the participant reports potential suicidal ideation outside the context of the Screening Enrollment Form or PHQ-9 assessment (e.g., through spontaneous expression, interaction with peer support specialists, or other clinical encounters). However, mental health resources will still be provided to participants in these cases, with additional response/follow-up dictated by site-specific SOPs.

11.8 Protocol Deviation Data

11.8.1 Protocol Deviation and Review Form

This form should be entered into the electronic data capture system whenever a protocol deviation occurs. This form will document a description of the deviation, how it occurred, the corrective action taken to resolve the specific deviation, as well as a description of the plan implemented to prevent future occurrences of similar deviations. This form will also capture if protocol deviations were a result of COVID-19 specific restrictions.

11.9 Substance Use Measures

11.9.1 Urine Drug Test

Urine testing for toxicology screening will be performed at baseline and at each follow-up visit to assess secondary outcomes. All specimens will be collected using point-of-care drug test kits following all the manufacturer's recommended procedures. Toxicology screens will test for the presence of commonly used drugs (including, but not limited to opiates, oxycodone, barbiturates, benzodiazepines, cocaine, amphetamines, methamphetamines, marijuana, methadone, buprenorphine, and fentanyl).

11.9.2 Readiness Ruler

This brief form will assess the participants readiness for and confidence in making a change to reduce overdose risk behaviors.

11.9.3 Tobacco Use History

The Tobacco Use History assessment will incorporate PhenX Core Tier 1 items. Tobacco use, including use of e-cigarettes and vaping, is assessed for lifetime use, quantity and frequency, and age of first use.

11.9.4 Fagerström Test for Nicotine Dependence [42]

This assessment is a brief, validated questionnaire to assess nicotine dependence, which will be collected to supplement the tobacco use history form being collected via the PhenX Toolkit assessment battery.

11.9.5 Cannabis Use Assessment

This form assesses use of marijuana/cannabis for medical purposes, marijuana exposure items, and medical issues or symptomology that marijuana is being used to treat/manage.

11.10 Weekly Mobile Surveys

Remote assessments via weekly mobile surveys will be kept brief to encourage compliance. Survey items (delivered via SMS text message to the participant and completed via REDCap) will include; self-reported opioid use, injection drug use, use/engagement in treatment or medications (MOUD), any use of other drugs or alcohol in the past week (yes/no), overdose risk behavior or mitigation (using drugs alone, Narcan access), and any prescription opioids used (prescribed or not).

11.11 PILOT Intervention

11.11.1 PILOT Intervention Activities Log

This form serves as the main log for the documentation of all peer-delivered interventions during the study. The PILOT peer support specialist will account for each contact attempted and connected with a participant and/or family/support person, check-off which interventions were performed, and quantify time spent on intervention(s). This form will also allow for weekly accounting of other peer activities such as presenting the participant in supervision; assessing participant's engagement and SUD status; and assessing participant's progress, response to treatment, and ongoing risks.

11.11.2 Supervisor Log

This form serves as the main log for the peer supervisor to document and assess each peer support specialist's participation in supervision as well as grade fidelity to the main components of the PILOT Intervention.

11.12 Study Site Surveys

TAU Characterization: The TAU characterization survey serves to document changes in sites' overdose ED TAU procedures throughout the study. Research staff will interview appropriate TAU or ED personnel who can speak to TAU procedures for this survey (i.e., TAU peers, ED staff, Site PIs, etc.). No identifying information will be collected on these surveys. Surveys will be completed

prior to site initiation, quarterly throughout the study, and once after enrollment and follow-up is completed. Individuals interviewed will provide verbal consent to speak with site research staff.

11.13 PILOT Peer Characterization

PILOT peers will be asked to complete two anonymous surveys, one asking about basic demographics and one regarding their training history, background, and perceptions and views on recovery and harm reduction. The second survey will ask personal questions about the peer's history, and again, will be anonymous. These data will be de-identified and captured in REDCap The second survey will be repeated at study completion. A public survey link will be sent to the peer's email address (all at the same time to avoid identifying any responses). One member of the research team will have access to the database and data will not be viewed until the end of study enrollment by any member of the lead research team. Peers do not need to complete the surveys if they do not feel comfortable, and the lead research team will not know who has responded. Language will be included in the survey to indicate that by completing the survey the Peer is providing consent.

12.0 TRAINING REQUIREMENTS

12.1 Overall

A comprehensive Training Plan will be developed by the Investigative Team to incorporate general training, study-specific training, mechanisms for competency assessment as well as a detailed description of training, supervision, and fidelity monitoring procedures. The Training Plan will include training and supervision specific to the PILOT peers, including instructional material and the PILOT intervention manual. The Investigative Team is responsible for the delivery of the training, with the team comprised of the Lead Node, CCC, DSC, as well as other participating nodes and subject matter experts, as applicable.

The CTN-0107 study staff will be trained as specified in the study Training Plan. Training will include Human Subjects Protection (HSP) and Good Clinical Practice (GCP) as well as protocol-specific training on assessments, study interventions, safety and targeted safety event reporting, study visits and procedures, data management, quality assurance, etc. The Lead Node is primarily responsible for development and delivery of study-specific training related to the study intervention(s) and procedures. The CCC is responsible for the development and delivery of non-intervention training, including regulatory and any laboratory procedures, safety and targeted safety event reporting, quality assurance and monitoring, etc. The DSC is responsible for training related to data management (DM), the electronic data capture system, and good DM practices. Other parties will contribute as needed based on the subject matter and material to be covered. The various sub-teams will collaborate to deliver quality instructional material designed to prepare research staff to fully perform study procedures based on the assigned research roles and responsibilities.

In addition to general and study-specific training, the Training Plan will include a description of the delivery methods to be used for each training module (e.g., via self-study, online, webcast, or teleconference). Study staff is required to complete institutionally required training per their research site, Institutional Review Board(s), and authorities with regulatory oversight. Tracking of training completion for individual staff as prescribed for assigned study role(s) will be documented, endorsed by the site Principal Investigator and the Lead Node, and audited by the CCC. As changes occur in the prescribed training, the Training Plan and training documentation tracking forms will be amended to reflect these adjustments.

12.2 Training, Supervision, and Fidelity Monitoring Procedures for Study Interventions

12.2.1 Selection of Interventionists/Care Facilitators

Three PILOT peer support specialists per site will be hired, with one peer specialist serving as the “Lead Peer.” The Lead Node will provide a sample job posting for Peer Support Specialists. Ideally, PILOT peers selected will be applicants who have: 1) experience as a peer support specialist; 2) familiarity with opioid use disorder and motivational interviewing approaches to substance use treatment; 3) knowledge of local resources for substance use treatment; and 4) a high comfort level in venturing out into the field not only to build and maintain rapport with care or

treatment agency staff, but also to locate study participants not following through with care or who are lost to follow-up.

Attention will be paid to hiring PILOT peers who represent the diversity that will be found in each site's substance using overdose population. The lead team will provide consultation as needed to local nodes and ED sites during the selection process.

12.2.2 Selection of Expert Trainers

The lead team is a varied group of investigators with depth and breadth of experience in OUD treatment, peer interventions for SUD and OD populations, and other peer, community engagement, and care coordination interventions, intervention training and supervision, and quality assurance (QA) monitoring. The lead team will also seek out consultants in designing and implementing the training (National Intervention Team). A training work group will be established and will be responsible for ensuring that the appropriate training is provided by the experienced lead team members.

12.2.3 Training of Certified Peer Support Specialists

All PILOT peers hired for the study will have already obtained a nationally recognized CPSS certificate (or equivalent based on the state). The study training of PILOT peers will occur in three phases: 1) pre-national training and pre-peer training; 2) in-person or remote peer training; and 3) post-peer and post-national training. The PILOT peers will also need to participate in the all-study national training, which will be virtual. The PILOT peer training will focus specifically on delivery of the intervention.

Pre-national training and pre-peer training will occur using conference calls, webinars, written materials, and self-study and will help prepare PILOT peers for the national training and trial launch. The pre-national training will provide instruction on the overall CTN-0107 study, creating an extensive local resource list for study participants and making connections in the community, making personal connections with key staff at all care and service agencies, and meeting participants in the community to deliver the PILOT intervention and connect participants with services.

The national training will occur in one location, in-person or virtually (if necessary), or a hybrid of virtual and in-person sessions. PILOT peer training will also occur specifically for training on the delivery of the intervention and related material. The peer training will include all PILOT peers and will provide didactic and experiential (role-play) training using the PILOT intervention manual. The training will include a discussion of PILOT peer roles, responsibilities, and boundaries; detailed overviews of each treatment group; appropriate communication techniques such as asking open-ended questions, paraphrasing, summarizing, and rolling with resistance; role-plays of various participant/care facilitator meetings with receipt of immediate feedback; and importance of active supervision.

Post-national training and post-peer training will occur via conference calls, webinars, and/or written materials with the purpose of providing additional support and guidance on intervention delivery and to assist Peers in preparing for trial launch.

12.2.4 Treatment Fidelity (Evaluation of Treatment Integrity)

Supervision of Staff Conducting the PILOT Intervention:

Given the spontaneous nature of peer-participant engagement and the fluidity of the PILOT intervention, PILOT intervention sessions will not be audio recorded. However, PILOT Peers will log all intervention activities as soon as possible after an intervention occurs in the Peer Intervention Log and Rolling Progress Note and present this log and note to supervisors during supervision. During supervision, supervisors will monitor and evaluate fidelity to the main components of the Intervention in the Supervisor Log, which will be scored and reviewed by the National Intervention Team, as well as supervisor notes that will also be reviewed. Feedback from supervision will be provided to the interventionist. The National Intervention Director will conduct regularly scheduled conference calls to discuss difficulties and successes in providing PILOT content; to facilitate learning from and supporting each other; and to facilitate receiving support and feedback from the National Intervention Director. Interventionists will be invited to seek additional consultation with the National Intervention Director via phone or email as intervention issues arise.

Quality Control of the PILOT Intervention:

Quality control of the PILOT intervention will be maintained through several methods: 1) since much of the contact PILOT peers may have with participants may occur off site and in the field where digitally recording sessions will not be appropriate, the Lead PILOT Peer or another qualified individual may randomly choose a day to shadow the PILOT peer out in the field and provide any necessary feedback; and 2) the Lead PILOT peer, study research staff, QA monitors, and/or lead study team members will routinely review the Peer Intervention Log to ensure that PILOT peers are engaging with study participants accordingly.

13.0 CONCOMITANT THERAPY/INTERVENTION

13.1 General

Prior to enrolling in CTN-0107, participants may have pre-existing relationships with professionals and paraprofessionals involved with SUD treatment, including a medical provider, CPSS, 12-step sponsor, and/or a social worker. Renewed or continued contact with any such professional or paraprofessional staff may include MOUD or other substance use disorder treatment. Regardless of study group, impeding any such contacts would be both unethical and infeasible. To account for non-study related professional or paraprofessional contacts, participants will be asked about such exposures during follow-up assessments.

14.0 STATISTICAL DESIGN AND ANALYSES

14.1 General Design

This study is a 2-arm, pragmatic, randomized, prospective pilot trial evaluating the effectiveness of PILOT compared with TAU on the frequency of self-reported overdose risk behaviors at 180 days after Index ED admission.

14.1.1 Study Hypothesis and Objectives

The primary hypothesis of this trial is that PILOT will result in a reduction in self-reported overdose risk behaviors at 180 days after Index ED admission as compared with TAU.

Key secondary hypotheses are that PILOT will result in a reduction of self-reported overdose risk behaviors at 30 days and 90 days, with the same hypothesis above, but at the different month time points.

The secondary objective of the trial includes the following:

1. Assess number of steps achieved along a modified SUD Cascade of Care for those randomized to PILOT vs. TAU.
2. Assess whether NFOO survivors within an ED setting are willing to engage in study procedures and with peer support services using the PILOT model and length of engagement and enrollment in PILOT among those randomized to pilot.

Exploratory objectives include the following. In situations of comparison between TAU and PILOT, the null hypothesis is that there is no difference between the two, and the alternative is that there is a difference.

1. Assess the effects of PILOT versus TAU on achievement of each individual step in the modified OUD Cascade of Care at 180 days, as well as 30 days and 90 days.

2. Evaluate the effectiveness of PILOT versus TAU of initiation on medications for OUD in the ED, among those participants with OUD.

3. Assess the effects of PILOT versus TAU on substance use frequency at 30-, 90-, and 180-days.

4. Evaluate the degree of engagement in Peer Support Services for participants randomized to PILOT at 30-, 90-, and 180-days, measured as number of contacts received or initiated with a Peer Support Specialist in the past month.

5. 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 during study participation.

6. Evaluate the effectiveness of PILOT versus TAU on percent of toxicology screens positive for opioids other than buprenorphine or methadone.

7. Evaluate the effectiveness of PILOT versus TAU on repeat non-fatal overdose and 210-day rates of death.

The primary outcome measure for the primary objective and key secondary hypotheses is the frequency of self-reported overdose risk behaviors at 180 days after Index ED admission as defined in **Section 7.1**, measured as a total score from 11 items ranging from 0 to 44.

The outcome measures for the secondary objectives are:

1. Number of steps achieved on the modified SUD Cascade of Care
2. Number accepting the intervention (to possibly engage with CPPSs using the PILOT model) compared with number approached
3. Length of time from baseline to last meeting with the PILOT intervention/counselor

Participants will be recruited at each ED site. Research staff assigned to the study will work during times to include evenings and weekends to ensure success with enrollment. Research staff will identify patients seen in the ED by screening, reviewing the ED trackboards, and by provider or peer referral. A member of the research team will keep a log of all patients screened and excluded and the reasons for exclusion. Potential participants identified will be evaluated by research staff for eligibility.

14.1.2 Randomization and Factors for Stratification

Eligible participants will be randomized in a 1:1 ratio to PILOT or TAU after confirmation of study eligibility status and baseline assessments have been completed. The randomization process will be performed by computer by the DSC. A permuted block randomization procedure with random block sizes will be implemented to balance per site and homelessness status (yes/no).

The randomization procedure will be conducted centrally through the DSC, and randomization details such as block size will not be conveyed to staff or participants. The DSC statistician will generate the randomization schedule using balanced blocks of varying sizes within strata to ensure lack of predictability along with relative equality of assignment across treatment groups. The DSC statistician will review 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 patient due to the intent-to-treat nature of the study.

14.2 Rationale for Sample Size and Statistical Power

Power analyses and sample size calculation was 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 form one used by Bohnert, et al (2016) [23]. 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 didn't 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.

14.3 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%
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%

		Total Sample Size		
Mean Score at Baseline	**Rate Ratio**	**100**	**125**	**150**
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 3: Power Results by RR

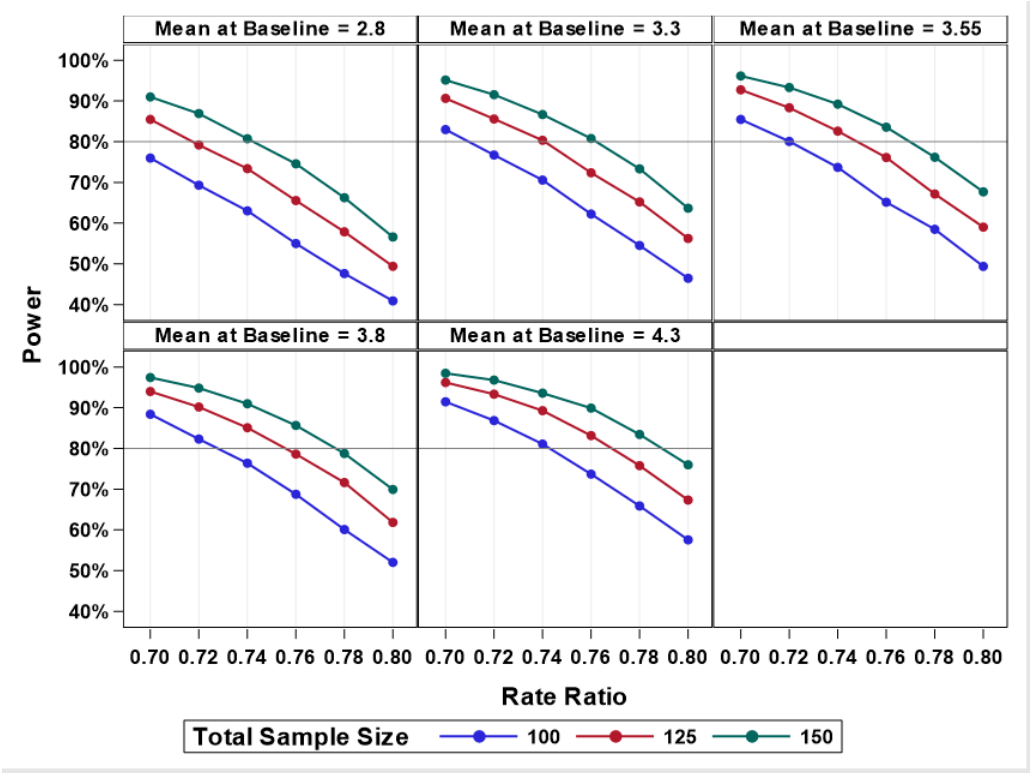
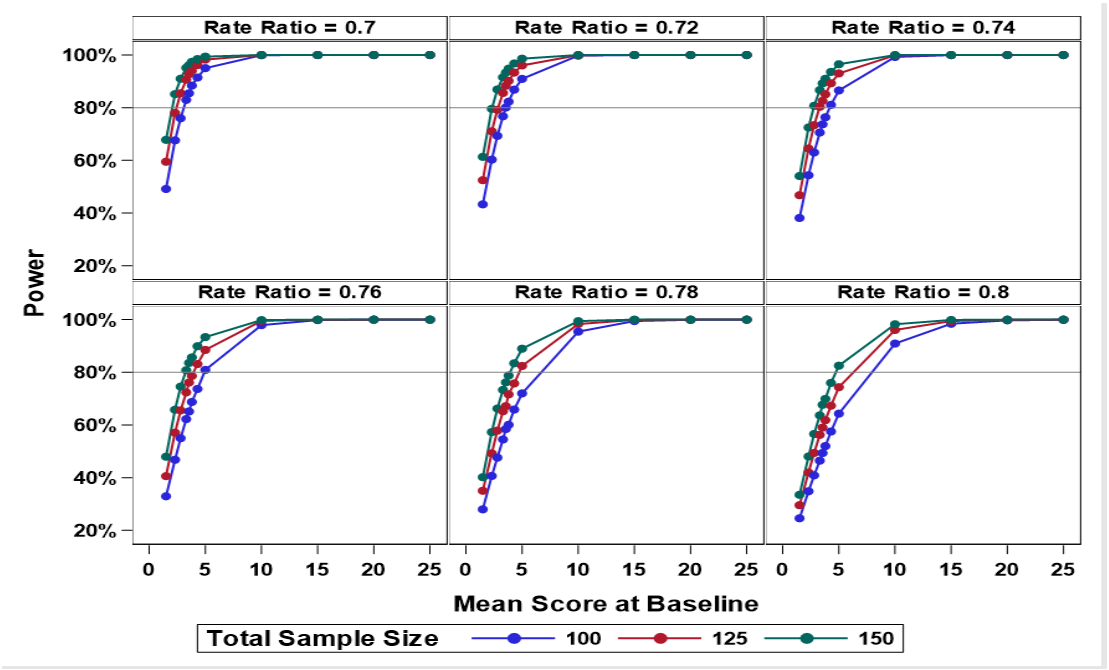


Figure 4: Power Results by Mean at Baseline



14.3.1 Projected Number of Sites

The anticipated and projected number of sites is three. This was chosen based on preliminarily-identified sites that had peer-led ED programs already instituted.

14.3.2 Projected Number of Participants per Site

This study will enroll a total of approximately 150 participants, for an expected number of approximately 50 per site.

14.4 Statistical Methods for Primary and Secondary Outcomes

Primary Outcome

The primary outcome of number of self-reported overdose risk behaviors at 180 days after Index ED admission, measured as the total score, will be analyzed with a longitudinal mixed effect Poisson regression model incorporating total score at earlier time points as well as 180 days. Fixed effect covariates for baseline score, treatment, days, site, stratum, and an interaction between treatment and days. Days will enter the model as a categorical covariate, as opposed to continuous, to allow greater flexibility. A random effect is included to account for correlation within each participant. The template SAS code to fit this model is given below.

```
pproc glimmix data = data;
        class site days participant;
        model risks = baseline trt|days site strat / dist = poisson link = log;
        random intercept / subject = participant;
run;
```

where data is the dataset, risks is the outcome, baseline is the participants risk behavior score at baseline, trt is a treatment indicator with a value of 1 indicating PILOT and 0 indicating TAU, days is the day number of the visit, and site and strat are variables corresponding to the participant's site and stratum level respectively.

The treatment effect of PILOT from this model will be given as a rate ratio (RR; as the exponential of the treatment and days interaction at 180 days plus the main effect of treatment) along with 95% confidence interval. This can be interpreted, conditionally, as a ratio of the mean risk behaviors for those assigned to PILOT divided by the mean risk behaviors for those assigned to TAU at 180 days, while all other variables (specifically including the baseline value) are the same. A value of 1 for the RR is the pivotal value. An RR of less than 1 would indicate less opioid risk behaviors for those assigned to PILOT compared to those assigned to TAU. A p-value will also be provided, testing whether there was a significant effect of PILOT versus TAU. If the p-value is strictly less than 0.05, there is a significant effect.

Key secondary hypotheses are this same outcome, but at 30 and 90 days, as opposed to 180 days. These will be analyzed in the same manner.

Secondary Outcomes

A secondary outcome is the number of steps achieved along a modified SUD Cascade of Care. This will be modeled similar to the primary outcome, an over dispersed 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 0 steps at baseline. Similar to the primary outcome, a RR along with 95% confidence interval and p-value will be given from this model to determine the effect and significance of PILOT as compared to TAU.

An important point to consider is that participants entering the trial may not have a primary diagnosis of OUD, or even SUD. Because of this, some steps are not inherently eligible to them at baseline. However, during the study, the participant may endorse OUD, or some SUD if none were at baseline, and become eligible for these steps. The approach taken here for the prespecified analysis method is that of protection/balanced by randomization. Participants entering without OUD, or no SUD, are likely to be balanced between treatment groups due to random assignment to treatment group (based on baseline DSM-5 SUD diagnoses), such that the effects of this would be equal between PILOT and FORCE. Additional supportive analyses, such as looking at OUD, SUD other than OUD, and no SUD subgroups as determined at baseline, are possible to examine possible chance imbalance between PILOT and FORCE.

For the other secondary outcomes, the number of participants approached and number who were willing to engage with CPPSs using the PILOT model, as well as 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.

14.5 Significance Testing

The primary outcome will be evaluated using a two-sided test with a type I error rate of 0.05, or 5%. The same procedure will be used for the key secondary hypothesis and the secondary outcome of number of steps achieved on the modified SUD cascade of care. No attempt will be made to adjust for multiple testing on the secondary outcomes as inference is focused on the single primary outcome 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.

14.6 Sensitivity and other Supportive Analyses

It will be helpful to characterize the distribution, and other characteristics, of the primary outcome to assist in planning future studies. Therefore, a model building process will be performed. Various count response regression models will be considered, including but not limited to:

- Poisson regression, with or without overdispersion
- Negative Binomial regression, with or without overdispersion
- Zero inflated Poisson regression
- Zero inflated Negative Binomial regression

The reasoning for including the Negative Binomial distribution-based regression is that it can account for over/under dispersion more directly than Poisson regression because it has a second parameter, as opposed to the Poisson distribution that is entirely specified by just one. Zero inflated versions of these are also considered because it is possible that a proportion of the participants will have a score of zero that is not in line with that specified by the Poisson or Negative Binomial distribution. A normal distribution may also be considered if the outcome appears to fit.

Whichever model is finally chosen for the outcome, based on model fitting quality (including deviance) and/or BIC, the effect of treatment will be assessed with an appropriate (for that model) 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 a RR from the model. In models with zero inflation, the role of treatment in the proportion of zeros will be summarized, along with an RR. Site will be included in the models as well as a random 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.

If changes to recruitment are made because of slow enrollment from EDs, an additional covariate indicating whether a participant was enrolled was initially defined from EDs, or otherwise, may be included to examine its effect on the outcomes.

14.7 Interim Analysis

A DSMB will monitor the progress of the trial. No interim analyses relating to futility or sample size re-estimation will be implemented in this pilot study.

14.8 Exploratory Analysis

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, will be reported 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 toxicology screens positive for primary substance of use will be summarized by proportion greater than 0%, mean, median, standard deviation, range (including minimum and maximum), and IQR (including 25th and 75th percentiles) 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 aren't overdose) may present a competing risk for death by overdose as well. As such, appropriate Fine and Gray models need be considered.

14.9 Missing Data and Dropouts

The prespecified primary outcome analysis method takes into account all available data so that special provisions are not needed for missing data. However, missing data handling methods, such as multiple imputation, may be considered as possible sensitivity analyses.

By definition, the secondary outcome of number of steps achieved on the modified SUD cascade of care will have no missing data. Either evidence was previously obtained that a step was achieved, or evidence was never collected that the step was achieved (and thus wasn't achieved).

14.10 Demographic and Baseline Characteristics

Baseline demographic and clinical variables will be summarized for participants enrolled in the active intervention phase of the trial. Descriptive summaries of the distribution of continuous baseline variables will be presented with percentiles (median, 25th and 75th percentiles), and with mean and standard deviation. Categorical variables will be summarized in terms of frequencies and percentages.

14.10.1 Subgroup Analyses

Per NIH policy, subgroup analyses will be implemented to assess whether sex, race, and/or ethnicity are feasibility or effect modifiers. The primary outcome results will be presented and tested (as applicable) within each demographic subgroup by including interactions with treatment assignment in the model.

14.11 Safety Analysis

The study's targeted safety events (ED visits, hospitalizations, non-fatal overdoses, and suicidal ideation) will be summarized in tabular form. A 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).

15.0 REGULATORY COMPLIANCE AND SAFETY

15.1 Statement of Compliance

This trial will be conducted in accordance with the current version of the protocol, in full conformity with the ethical principles outlined in the Declaration of Helsinki, the Protection of Human Subjects described in the International Council for Harmonization Good Clinical Practice (GCP) Guidelines, applicable United States (US) Code of Federal Regulations (CFR), the NIDA Terms and Conditions of Award, and all other applicable state, local, and federal regulatory requirements. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. An Operations Manual will be provided as a reference guide and study quality assurance tool.

15.2 Institutional Review Board Approval

Prior to initiating the study, participating site investigators will obtain written approval from their Institutional Review Board (IRB) to conduct the study at their respective site, and reliance agreements will be initiated and executed for a single IRB for this study. The MUSC IRB will serve as the IRB of record for this multi-site study. If changes to the study protocol become necessary, protocol amendments will be submitted in writing by the investigators for IRB approval prior to implementation. In addition, IRBs will approve all consent forms, recruitment materials and procedures, and any materials given to the participant, and any changes made to these documents throughout study implementation. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. For changes to the consent form, a decision will be made regarding whether previously consented participants need to be re-consented. IRB continuing review will be performed annually, or at a greater frequency contingent upon the complexity and risk of the study. Each site principal investigator is responsible for maintaining copies of all current IRB approval notices, IRB-approved consent documents, and approval for all protocol modifications. These materials must be received by the investigator prior to the initiation of research activities at the site and must be available at any time for audit. Unanticipated problems involving risk to study participants will be promptly reported to and reviewed by the IRB of record, according to its usual procedures.

MUSC IRB will be the IRB of record for the protocol and will provide study oversight in accordance with 45 CFR 46. Participating institutions have agreed to rely on MUSC IRB and have entered into reliance/authorization agreements for Protocol CTN-0107. MUSC IRB will follow written procedures for reporting its findings and actions to appropriate officials at each participating institution. Some sites may meet Exception Criteria to the NIH sIRB Policy and may not utilize the IRB of Record.

15.3 Informed Consent

The informed consent process is a means of providing study information to each prospective participant and allows for an informed decision about participation in the study. Informed consent continues throughout the individual's study participation. The informed consent form(s) will include

all the required elements of informed consent and may contain additional relevant consent elements and NIDA CCTN specific additional elements. Each study site must have the study informed consent(s) approved by the IRB of record. Prior to initial submission to the IRB and with each subsequent consent revision, the consent form(s) must be sent to the Clinical Coordinating Center (CCC) and the Lead Node (LN) to confirm that each consent form contains the required elements of informed consent as delineated in 21 CFR 50.25(a) and CFR 46.116(b), as well as pertinent additional elements detailed in 21 CFR 50.25(b) and 45 CFR 46.116(c) and any applicable CCTN requirements. Every study participant is required to sign a valid, IRB-approved current version of the study informed consent form prior to the initiation of any study related procedures. The site must maintain the original signed informed consent for every participant in a locked, secure location that complies with all applicable IRB and institutional policies and that is accessible to the study monitors. Every study participant should be given a copy of the signed consent form. As a back-up method to in-person informed consent procedures, study sites will use REDCap eConsent, if in person consent is not possible for a particular participant.

During the informed consent process, research staff will explain the study to the potential participant and provide the potential participant with a copy of the consent form to read and keep for reference. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and their rights as research participants. Extensive discussion of risks and possible benefits will be provided to the participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family and close friends or think about it prior to agreeing to participate. If the participant is interested in participating in the study, a qualified staff member will review each section of the IRB-approved informed consent form in detail and answer any questions the participant may pose. The participant, or participant's legally authorized representative, will consent by signing and dating the consent document. The person obtaining consent and a witness, if required by the IRB of record, will also sign and date the consent document. It is strongly recommended that another research staff member review the consent after it is signed to ensure that the consent is properly executed and complete. Staff members delegated by the PI to obtain informed consent must be listed on the Delegation of Responsibility and Staff Signature Log and must be approved by the IRB, if required. All persons obtaining consent must have completed appropriate GCP and Human Subjects Protection training, as mandated by NIDA standard operating procedures.

As a backup method, REDCap electronic consent (e-consent), combined with a HIPAA-secure video conferencing platform, will be used during the consent process (preferred). Participants are also able to view the informed consent document on a computer or phone via REDCap and complete a phone call with research staff. Video chat functionality will only be used if all parties have the availability and is not required for consent to be performed. Approved research staff members will have an MUSC external NetID, which allows them to access MUSC's version of REDCap. Each study site will have their own MUSC REDCap eConsent database managed by the lead research team and only approved users for the study will have access. Using these systems, signatures on the consent form may be obtained electronically via REDCap.

The informed consent form must be updated or revised whenever important new safety information is available, or whenever the protocol is amended in a way that may affect participants' participation in the trial. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The participant will be informed that their participation is voluntary, and they may withdraw from the study at any time, for any reason without penalty. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice. Study sites will be responsible for maintaining signed consent forms as source documents for quality assurance review and regulatory compliance.

15.4 Quality Assurance Monitoring

In accordance with federal regulations, the study sponsor is responsible for ensuring proper monitoring of an investigation and ensuring that the investigation is conducted in accordance with the protocol. Qualified monitors will oversee aspects of site conformity to make certain the site staff is operating within the confines of the protocol, and in accordance with GCP. This includes but is not limited to protocol compliance, documentation auditing, and ensuring the informed consent process is being correctly followed and documented. Non-conformity with protocol and federal regulations will be reported as a protocol deviation and submitted to the study sponsor and study IRB of record, (as applicable), for further review.

Investigators will host periodic visits by NIDA contract monitors who will ensure all study procedures are conducted, site and study SOPs are followed, and that study data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulations. These monitors will audit, at mutually agreed upon times, regulatory documents, CRFs, and corresponding source documents for each participant. Monitors will have the opportunity and ability to review any study-associated document or file.

NIDA-contracted monitors will assess whether submitted data are accurate and in agreement with source documentation and will also review regulatory/essential documents such as correspondence with the IRB. Areas of particular concern will be participant informed consent forms, protocol adherence, reported safety events and corresponding assessments, and PI oversight and involvement in the trial. Reports will be prepared following the visit and forwarded to the site PI, the Lead Investigator (LI), and NIDA Center for Clinical Trials Network (CCTN).

Qualified node personnel (Node Protocol Managers and/or Quality Assurance (QA) monitors) or other designated party(ies) will provide site management for each site during the trial. Node QA personnel or other designated party(ies) will audit source documentation, including informed consent forms and HIPAA forms. This will take place as specified by the local protocol team, node PI or lead team and will occur as often as needed to help prevent, detect, and correct problems at the study sites. Node QA personnel will verify that study procedures are properly followed and that site staffs are trained and able to conduct the protocol appropriately. If the node staff's review of study documentation indicates that additional training of study personnel is needed, node staff will undertake or arrange for that training. Details of the contract, node QA and data monitoring are found in the study QA monitoring plan.

15.5 Participant and Data Confidentiality

Participant confidentiality and privacy are strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency, and will be maintained in accordance with all applicable federal regulations and/or state/Commonwealth law and regulations. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team, unless such disclosures are required by law or, when the study clinician is not readily available, there is concern that urgent clinical assessment is needed to protect the participant's personal safety or welfare. In these cases, researchers may need to disclose medical and health-related research data to authorities and/or non-study care providers. Other than these exceptions, no personally identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency and the participant.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Participant records will be held confidential using study codes for identifying participants on CRFs, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as denoted in **Section 15.11, Records Retention and Requirements**.

By signing the protocol signature page, the investigator affirms that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB/Privacy Board, Ethical Review Committee, or similar expert committee, and/or to the affiliated institution and its employees, only under an appropriate understanding of confidentiality with such board or committee, and/or affiliated institution and its employees.

15.5.1 Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical, or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see https://humansubjects.nih.gov/coc/index). This protects participants from disclosure of sensitive information (e.g., drug use). It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or

in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

15.5.2 Health Information Portability Accountability Act (HIPAA)

Study sites may be required by their institutions to obtain authorization from participants for use of protected health information. Sites will be responsible for communicating with their IRBs or Privacy Boards and obtaining the appropriate approvals or waivers to be in regulatory compliance. Releases of participant identifying information that are permitted by the HIPAA regulations, but which are prohibited by other applicable federal regulations and/or state/Commonwealth law and regulation, are prohibited.

15.6 Investigator Assurances

Each site must have on file an active Federalwide Assurance (FWA) with the HHS Office for Human Research Protection setting forth the commitment of the organization to establish appropriate policies and procedures for the protection of human research subjects in alignment with 45 CFR 46, Subpart A, with documentation sent to NIDA or its designee. Research covered by these regulations cannot proceed in any manner prior to NIDA receipt of certification that the research has been reviewed and approved by the IRB provided for in the assurance (45 CFR 46.103). Prior to initiating the study, the principal investigator at each study site will sign a protocol signature page and investigator agreement, providing assurances that the study will be performed according to the standards stipulated therein.

15.6.1 Financial Disclosure/Conflict of Interest

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. Everyone with decision-making responsibilities regarding the protocol will confirm to the sponsor annually that they have met their institutional financial disclosure requirements.

15.7 Clinical Monitoring

Investigators will host periodic visits by NIDA contract monitors who will examine whether study procedures are conducted appropriately, and that study data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulations. These monitors will audit, at mutually agreed upon times, regulatory documents, case report forms (CRFs), informed consent forms and corresponding source documents for each participant. Monitors will have the opportunity and ability to review any study-associated document or file.

NIDA-contracted monitors will assess whether submitted data are accurate and in agreement with source documentation and will also review regulatory/essential documents such as correspondence with the IRB. Areas of particular concern will be participant informed consent forms, protocol adherence, reported safety events and corresponding assessments, and principal investigator oversight and involvement in the trial. Reports will be prepared following the visit and forwarded to the site principal investigator, the lead investigator and NIDA CCTN.

Qualified node personnel (Node QA monitors) or other designated party(ies) will provide site management for each site during the trial. Node QA staff or other designated party(ies) will audit source documentation, including informed consent forms and HIPAA forms. This will take place as specified by the local protocol team, node PI or lead team and will occur as often as needed to help prevent, detect, and correct problems at the study sites. Node QA personnel will verify that study procedures are properly followed and that site personnel are trained and able to conduct the protocol appropriately. If the node personnel's review of study documentation indicates that additional training of site study personnel is needed, node QA personnel will undertake or arrange for that training. Details of the contract, node QA and data monitoring are found in the study QA monitoring plan.

15.8 Inclusion of Women and Minorities

The study sites should aim and take steps to enroll a diverse study population. The rates of women and minorities enrolled will depend on sites selected to participate and their ED admissions of NFOO. The study will aim to enroll 30-40% women in the trial and 20-25% racial and ethnic minorities. If difficulty is encountered in recruiting an adequate number of women and/or minorities, the difficulties involved in recruitment will be discussed in national conference calls and/or face-to-face meetings, encouraging such strategies as linkages with medical sites and or treatment programs that serve a large number of women and/or minorities, advertising in newspapers or radio stations with a high female/minority readership/listening audience, etc.

15.9 Prisoner Certification

As per 45 CFR 46 Subpart C, there are additional protections pertaining to prisoners as study participants. A prisoner is defined as any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing. To meet these additional protections, the study team will obtain certification from the Office for Human Research Protections (OHRP) to follow-up with participants who become prisoners during the study, as necessary.

Participants in this study will be individuals with a history of substance use, misuse, and opioid-related overdose. Participants may be at a greater risk of becoming involved with the criminal justice system. In accordance with exclusion criterion #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)"], this study will not enroll participants currently involved with the criminal justice system. However, there is a chance that during the study, a participant could become incarcerated or otherwise meet the definition of a prisoner (as delineated in 45 CFR 46.303(c)). Those participants who become incarcerated during their involvement with this study will continue to be followed to ensure safety and data integrity (following OHRP approval and with compliance to local state and country rules and restrictions).

Prisoner contact guidelines: All study sites will follow the same guidelines surrounding contact with enrolled participants who become incarcerated. Detailed local SOPs will be developed by

individual sites, based on the rules within their state. Local SOPs will be reviewed and approved by the lead research team prior to any prisoner contact. All sites will follow these general guidelines: 1) the site (inclusive of RA/RCs and PILOT peers, when applicable) will not contact any participants who become incarcerated or detained within the criminal justice system unless the participant gives permission for the site staff to contact them (obtained following informed consent with a release of information and agreement to be contacted should they become incarcerated), 2) the study site (inclusive of RA/RCs and PILOT Peers) may also use IRB-approved language that can be sent to the detention facility requesting permission to contact the study participant to set up a time for a follow-up research study visit and visit from the PILOT Peer (as applicable), 3) study participants will not be compensated for completing study procedures while they are incarcerated. If permitted by state/local regulations, the site may defer compensation for study procedures completed while the participant is incarcerated until the participant is no longer considered a prisoner (see local SOPs for site-specific details and procedures for deferred compensation), 4) if a study participant becomes incarcerated, study staff (inclusive of RA/RCs and PILOT Peers) must adhere to local restrictions at that particular facility regarding contact and research participation, 5) in-person visits, telephone calls, video chat, etc. will be allowed to maintain rapport and/or collect study visit data. Contact and rapport building can be done on non-secured lines and/or in monitored rooms being mindful of sensitive information and safety. Any research data collection must only be obtained through secure means (e.g., in a private room where not being recorded and/or on a secure line, etc.).

15.10 Regulatory Files

The regulatory files should contain all required regulatory documents, study-specific documents, and important communications. Regulatory files will be checked at each participating site for regulatory document compliance prior to study initiation, throughout the study, as well as at study closure.

15.11 Records Retention and Requirements

Research records for all study participants (e.g., case report forms, source documents, signed consent forms, audio and video recordings [if applicable], and regulatory files) are to be maintained by the investigator in a secure location for a minimum of 3 years after the study is completed and closed. These records will also be maintained in compliance with IRB, state, or federal requirements, whichever is longest. The Sponsor and Lead Investigator must be notified in writing and acknowledgment from these parties must be received by the site prior to the destruction or relocation of research records.

15.12 Reporting to Sponsor

The site principal investigator agrees to submit accurate, complete, legible, and timely reports to the Sponsor, as required. These include, but are not limited to, reports of any changes that significantly affect the conduct or outcome of the trial or increase risk to study participants. Safety reporting will occur as previously described. At the completion of the trial, the Lead Investigator will provide a final report to the Sponsor.

15.13 Audits

The Sponsor has an obligation to ensure that this trial is conducted according to good clinical research practice guidelines and may perform quality assurance audits for protocol compliance. The Lead Investigator and authorized staff from the Southern Consortium Node; the National Institute on Drug Abuse Clinical Trials Network (NIDA CTN, the study sponsor); NIDA's contracted agents, monitors or auditors; and other agencies such as the Department of Health and Human Services (HHS), the Office for Human Research Protection (OHRP) and the Institutional Review Board of record may inspect research records for verification of data, compliance with federal guidelines on human participant research, and to assess participant safety.

15.14 Study Documentation

Each participating site will maintain appropriate study documentation (including medical and research records) for this trial, in compliance with ICH E6 R2 and regulatory and institutional requirements for the protection of confidentiality of participants. Study documentation includes all case report forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, Ethics Review Committee or Institutional Review Committee correspondence and approved consent form and signed participant consent forms. As part of participating in a NIDA-sponsored study, each site will permit authorized representatives from NIDA and regulatory agencies to examine (and when permitted by law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable if it is a clear, legible, and exact duplication of the original document.

15.15 Protocol Deviations

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

Any departure from procedures and requirements outlined in the protocol will be classified as either a major or minor protocol deviation. The difference between a major and minor protocol deviation has to do with the seriousness of the event and the corrective action required. A minor protocol deviation is considered an action (or inaction) that by itself is not likely to affect the

scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Major protocol deviations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or the integrity of study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Sites will be responsible for developing corrective action plans for both major and minor deviations as appropriate. Those corrective action plans may be reviewed/approved by the Lead Node and the CCC with overall approval by the IRB of record as needed. All protocol deviations will be monitored at each site for (1) significance, (2) frequency, and (3) impact on the study objectives, to ensure that site performance does not compromise the integrity of the trial.

All protocol deviations will be recorded in the Electronic Data Capture (EDC) system via the Protocol Deviation CRF. The CCC, DSC and the Lead Investigator must be contacted immediately if an unqualified or ineligible participant is randomized into the study.

Additionally, each site is responsible for reviewing their local IRB's definition of a protocol deviation or violation and understanding which events need to be reported. Sites must recognize that the CTN and IRB definition of a reportable event may differ and act accordingly in following all reporting requirements for both entities.

15.16 Safety Monitoring

Given the low-risk nature of the PILOT intervention and this study, only select Adverse Events (AEs) and Serious Adverse Events (SAEs), collectively termed Safety Events will be tracked and reported during this study. Accordingly, Safety Events associated with participant death, post-index overdoses, ED visits, and hospitalizations will be solicited during the 30-, 90-, 180-, and 210-day visits (or in-between visits if reported spontaneously). Other AEs and SAEs will not be solicited, documented, or reported in the data system during this protocol. Reporting timeframes for Safety Events will follow regulatory requirements. While active suicidal ideation at the screening visit is considered an exclusion criterion, participant suicidal ideation occurring after enrollment will be addressed in accordance with **Section 11.7.1**.

The Lead Investigator (LI) and Site PI will review or provide consultation for relevant Safety Events as needed. These reviews will include an assessment of the possible relatedness of the event to the study intervention or other study procedures. The Site PI will also provide advice for decisions to exclude, refer, or withdraw participants as required. In addition, NIDA will assign a Safety Monitor/Medical Monitor to this protocol to independently review the safety data, present it to the DSMB for periodic review, and provide PIs a Safety Letter when necessary. The Safety Monitor/Medical Monitor will determine which Safety Events require expedited reporting to NIDA, the DSMB and regulatory authorities. This will include events that are serious, related, and unexpected. The study staff will be trained to monitor for and report Safety Events.

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

15.16.1 Data and Safety Monitoring Board (DSMB)

An independent CTN DSMB will examine accumulating data to assure protection of participants' safety while the study's scientific goals are being met. The CTN DSMB is responsible for conducting periodic reviews of accumulating safety and efficacy data. It will determine whether there is support for continuation of the trial, or evidence that study procedures should be changed, or if the trial should be halted, for reasons relating to the safety of the study participants, the efficacy of the treatment under study, or inadequate trial performance (e.g., poor recruitment).

15.16.2 Safety Monitor/Medical Monitor

The CCC Safety Monitor/Medical Monitor is responsible for reviewing all Safety Events reported. Where further information is needed, the Safety Monitor/Medical Monitor will discuss the Safety Event with the site. Reviews of Safety Events will be conducted in the Advantage eClinical data system and will be a part of the safety database. All Safety Events will be reviewed on a regular basis to observe trends or unusual events.

The CCC Safety Monitor/Medical Monitor will in turn report Safety Events to the sponsor and regulatory authorities if the event meets the definition of an expedited event. Reports will be generated and presented for Data Safety Monitoring Board (DSMB) meetings.

15.16.3 Safety Events

For the purposes of this protocol, the collection and reporting of the following Safety Events are not required in the data system:

- Pregnancy
- Admission for detoxification
- Elective hospitalization

16.0 DATA MANAGEMENT

16.1 Design and Development

This protocol will utilize a centralized Data and Statistics Center (DSC). The DSC will be responsible for development of the electronic case report forms (eCRFs), development and validation of the clinical study database, ensuring data integrity, and training site and participating node staff on applicable data management procedures. Advantage eClinical, Qualtrics^{XM}, and REDCap entry systems will be implemented. These systems will be developed to ensure that guidelines and regulations surrounding the use of computerized systems used in clinical trials are upheld. Advantage eClinical will be developed by the DSC and will be used for study visit ePRO assessments and research staff administered assessments. The Qualtrics^{XM} system will be used by the research staff to complete the Screening Exit Survey for participants that refuse to be in the study or are otherwise ineligible. The REDCap system will be developed and managed by the Lead Node, which will be used for participants to complete their weekly surveys. The remainder of this section provides an overview of the data management plan associated with this protocol. The DSC will receive the REDCap weekly survey data regularly throughout the trial, will conduct data quality activities (to the extent feasible on participant entered data), and will be responsible for data analysis. For the REDCap TAU Characterization and Peer Surveys, the DSC will receive this de-identified data only at the end of the trial due to the limited nature of confidentiality possible on these assessments, and DSC will not be responsible for analyzing these data.

16.2 Site Responsibilities

The data management responsibilities of each individual site will be specified by the DSC and outlined in a User's Guide.

16.3 Data Center Responsibilities

The DSC will 1) develop a data management plan and will conduct data management activities in accordance with that plan, 2) provide final guided source documents and eCRFs for the collection of all data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) conduct ongoing data monitoring activities on study data from all participating sites, 5) monitor any preliminary analysis data cleaning activities as needed, and 6) rigorously monitor final study data cleaning.

16.4 Data Collection

The data collection process consists of direct data entry at the study sites into the Advantage eClinical Electronic Data Capture systems (EDC). If Advantage eClinical is not available, the DSC will provide the sites with a final set of guided source documents and completion instructions. Data entry into Advantage eClinical should be completed according to the instructions provided and protocol specific training. The investigator is responsible for maintaining accurate, complete, and up-to-date records, and for ensuring the completion of the eCRFs for each research participant.

16.5 Data Acquisition and Entry

Completed forms and electronic data will be entered into Advantage eClinical in accordance with the User's Guide. Only authorized individuals shall have access to eCRFs.

16.6 Data Editing

Completed data will be entered into Advantage eClinical. If incomplete or inaccurate data are found, a query will be generated to the sites for a response, though queries for missing data will not be generated for mobile surveys. Site study staff will resolve data inconsistencies and errors and enter all corrections and changes into Advantage eClinical.

16.7 Data Transfer/Lock

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DSC. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical site staff and by DSC staff will be secured and password protected.

Data will be transmitted by the DSC to the NIDA central data repository as requested by NIDA. The DSC will conduct final data quality assurance checks and "lock" the study database from further modification. The final analysis dataset will be returned to NIDA, as requested, for storage and archive.

16.8 Data Training

The training plan for site staff includes provisions for training on assessments, eCRF completion guidelines, data management procedures, and the use of Advantage eClinical or other applicable EDC systems.

16.9 Data Quality Assurance

To address the issue of data entry quality, the DSC will follow a standard data monitoring plan. An acceptable quality level prior to study lock or closeout will be established as a part of the data management plan. Data quality summaries will be made available during the protocol.

17.0 DATA SHARING, PUBLIC ACCESS, AND PUBLICATIONS

This study will comply with the NIH Data Sharing Policy and Implementation Guidance (https://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm) and the HEAL Public Access and Data Sharing Policy (https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative/research/heal-public-access-data-sharing-policy).

Investigators will also register and report results of the trial in ClinicalTrials.gov, consistent with the requirements of the Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration (https://grants.nih.gov/policy/clinical-trials/reporting/understanding/nih-policy.htm).

Primary data for this study will be available to the public in the NIDA data repository, per NIDA CTN policy. An exception to data sharing is for data collected at the site level, which cannot be sufficiently de-identified given only three participating sites. Data that characterizes treatment as usual for the study site will not be shared on the NIDA data repository. Additionally, data collected to characterize the PILOT Peers will not be shared on the NIDA data repository as this information may contain sensitive information and cannot be sufficiently de-identified. For more details on data sharing please visit https://datashare.nida.nih.gov/.

The primary outcome publication will be included along with study underlying primary data in the data share repository, and it will also be deposited in PubMed Central http://www.pubmedcentral.nih.gov/ per NIH Policy (http://publicaccess.nih.gov/).

The planning, preparation, and submission of publications will follow the policies of the Publications Committee of the CTN. Considerations for ensuring confidentiality of any shared data are described in **Section 15.5.**

18.0 PROTOCOL SIGNATURE PAGE

SPONSOR'S REPRESENTATIVE (CCTN SCIENTIFIC OFFICER OR DESIGNEE)

Printed Name	Signature	Date

ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version 6.0 of the protocol and agree to conduct this clinical study in accordance with the design and provisions specified therein.
- I agree to follow the protocol as written except in cases where necessary to protect the safety, rights, or welfare of a participant, an alteration is required, and the sponsor and IRB have been notified prior to the action.
- I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.
- I agree to personally conduct or supervise this investigation at this site and to ensure that all site staff assisting in the conduct of this study are adequately and appropriately trained to implement this version of the protocol and that they are qualified to meet the responsibilities to which they have been assigned.
- I agree to comply with all the applicable federal, state, and local regulations regarding the obligations of clinical investigators as required by the Department of Health and Human Services (DHHS), the state, and the IRB.

SITE'S PRINCIPAL INVESTIGATOR

Printed Name	Signature	Date

Clinical Site Name _____

Node Affiliation _____

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20.0 APPENDIX A: DATA AND SAFETY MONITORING PLAN (DSMP)

BRIEF STUDY OVERVIEW. The primary objective of the CTN-0107 (PILOT) study is to advance understanding and improve outcomes for individuals who have experienced a recent non-fatal overdose involving opioids (NFOO). The study will recruit individuals from Emergency Department (ED) after surviving a NFOO in the past 72 hours or from the community who have experienced a NFOO in the past 30 days. The preliminary effectiveness of a specialized peer recovery intervention tailored for overdose survivors, called **P**eer **I**ntervention to **L**ink **O**verdose survivors to **T**reatment (PILOT), will be evaluated as compared to treatment as usual (TAU) in the ED to determine if the PILOT intervention reduces risk of future overdoses compared to TAU.

The PILOT study is a prospective, randomized, controlled preliminary trial that will recruit approximately 150 overdose survivors from three ED sites in the United States. Participants will be approached and randomized during their ED visit. To be eligible, participants must have had an opioid-related overdose in the past 30 days. If they are presenting in the ED for another issue, they may still be eligible for the study. Participants will be randomized 1:1 to either the PILOT intervention or TAU. Participants will complete study visits at 30-, 90-, and 180-days, as well as a follow-up visit at 210-days. The primary hypothesis is that participants randomized to PILOT will have reduced overdose risk compared to those randomized to TAU based on an overdose risk behavior scale. Secondarily, the study will assess: 1) whether NFOO survivors within an ED setting are willing to engage with Certified Peer Support Specialists (CPSS) using the PILOT model, and 2) if participants randomized to PILOT engage in more steps in a substance use disorder cascade of care and engagement in treatment.

1.0 OVERSIGHT OF CLINICAL RESPONSIBILITIES

A. Site Principal Investigator

Each participating site's Principal Investigator (PI) is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified, trained research staff and medical clinicians to assess, report, and monitor adverse events.

Targeted Safety Events occurring during the clinical trial will be collected, documented, and reported by the investigator or sub-investigators according to the Protocol.

Reportable Safety Events should ideally be entered into the data system within 48 hours of the site staff becoming aware of the event, but no later than within 7 days of site awareness. Death-related Safety Events are required to be entered into the data system within 24 hours of site's knowledge of a confirmed death event.

B. CCC Safety Monitor/Medical Monitor

The NIDA CTN Clinical Coordinating Center's (CCC) Safety Monitor/Medical Monitor or designee is responsible for reviewing all Safety Events reported. The CCC Safety Monitor/Medical Monitor is alerted via email each time a death event is reported in the EDC system. All death events will be reviewed at the time they are reported in the EDC system. Where further information is needed, the Safety Monitor/Medical Monitor or designee will discuss the event with the site staff. Reviews

of Safety Events by the CCC Safety Monitor/Medical Monitor or designee will be documented in the safety database. All Safety Events are reviewed on a weekly basis to observe trends or unusual events.

Voluntary Regulatory Reporting in non-IND Trials:

For non-IND trials, if an event meets expedited reporting criteria (serious, related, and unexpected) the CCC Safety Monitor/Medical Monitor or designee will voluntarily report to FDA/Regulatory Authorities using the MedWatch Form 3500 or similar.

C. Data and Safety Monitoring Board (DSMB)

The NIDA CTN DSMB affiliated with this trial will be responsible for conducting periodic reviews of accumulating safety, trial performance, and outcome data. Reports will be generated and presented for Data and Safety Monitoring Board (DSMB) meetings. The DSMB will receive listings of Safety Events, to include deaths, at a frequency requested by the DSMB, but at least annually. Furthermore, the DSMB will be informed of any expedited Safety Event reporting. The DSMB will make recommendations to NIDA CCTN as to whether there is sufficient support for continuation of the trial, evidence that study procedures should be changed, or evidence that the trial (or a specific site) should be halted for reasons relating to safety of the study participants or inadequate trial performance (e.g., poor recruitment).

Following each DSMB meeting, the NIDA CCTN will communicate the outcomes of the meeting, based on DSMB recommendations, in writing to the study Lead Investigator. This communication summarizing study safety information will be submitted to participating IRBs.

D. Quality Assurance (QA) Monitoring

The monitoring of the study site(s) will be conducted on a regular basis using a combination of NIDA CCTN CCC monitors (if applicable) and the Local Node QA Monitors (if applicable). Investigators will host periodic visits for the monitors. The purpose of these visits is to assess compliance with GCP requirements and other applicable regulatory requirements, as well as to document the integrity of the trial progress. The investigative site will provide direct access to all trial related sites (e.g., pharmacy, research office), source data/documentation, and reports for the purposes of monitoring and auditing by the monitors, as well as for the inspection by local and regulatory authorities. Areas of particular concern will be the review of inclusion/exclusion criteria, participant Informed Consent Forms, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents, participant records, and Principal Investigator supervision and involvement in the trial. The monitors will interact with the site staff to identify issues and re-train the site as needed to enhance research quality.

Site Visit Reports will be prepared by the NIDA CCC monitors following each site visit. These reports will be sent to the site Principal Investigator, the study Lead Investigator and NIDA CCTN.

Local Node QA site visit reports will be prepared following each site visit, as applicable. These reports are sent to those entities required of them by the Lead Investigative team, generally

including the Lead Investigator, site Principal Investigator, Node PI and a CCC representative, usually the protocol specialist for the study.

E. Management of Risks to Participants

Confidentiality

Confidentiality of participant records will be secured by the use of study codes for identifying participants on CRFs, and secure storage of any documents that have participant identifiers on-site, as well as secure computing procedures for entering and transferring electronic data. The documents or logs linking the study codes with the study participant on-site will be kept locked/securely stored separately from the study files and the medical records. No identifying information will be disclosed in reports, publications or presentations.

Information Meeting Reporting Requirements

The consent form will specifically state the types of information that are required for reporting and that the information will be reported as required. These include suspected or known sexual or physical abuse of a child or elders, or threatened violence to self and/or others.

Participant Protection

The site's study clinician or other designated and qualified individual will evaluate all pertinent screening and baseline assessments prior to participant randomization to ensure that the participant is eligible and safe to enter the study. Safety Events will be assessed and documented at each study visit. Individuals who experience a Safety Event that compromises safe participation in a study will be discontinued from further study intervention and provided referrals for other treatment or to specialized care. Study personnel will request that the participant complete an end-of-intervention visit to assure safety and to document end-of-intervention outcomes.

Pregnancy

As there is no medication intervention, pregnancy will not be followed within the context of this study.

Study Specific Risks

The potential risks associated with study participation are minimal. There is a risk of loss of confidentiality of personal information as a result of participation in this study. To mitigate this risk and ensure confidentiality, participants will be given a de-identified study code (participant ID), and data and CRFs will be stored in secure databases and kept in locked/securely stored research offices. Only designated study staff will have access to research materials.

There is the potential risk for the interview questions and/or assessments to evoke emotional discomfort or distress for participants when they are asked to recall past situations that were unpleasant or distressing (e.g., past overdoses). This is unlikely to be serious in nature, however, participants will be given the opportunity to refuse to answer questions.

There is also the potential for discomfort, distress, or annoyance if a participant is lost or unresponsive to research staff or PILOT peer contact attempts. The PILOT program is based on assertive community engagement and re-engagement, when participants/patients are lost or are not engaging in the intervention. The PILOT peer will take steps to re-engage the participant, when necessary. Re-engagement will include multiple attempts and forms of communication to the participant as well as reaching out to family and friends to get in touch with the participant (their contact information will be provided during the screening visit). Some participants may experience discomfort or frustration during this re-engagement process. However, participation in this study is voluntary and participants can withdraw their consent from the study at any time. If that occurs, the research team and PILOT peer would no longer contact or engage the participant in the intervention.

There is the potential for unknown risks to occur during the study. If any additional risks arise that may affect the subject's decision to participate, the research team will inform the subjects.

2.0 DATA MANAGEMENT PROCEDURES

This protocol will utilize a centralized Data and Statistics Center (DSC). A web-based distributed data entry model will be implemented. These electronic data capture systems (Advantage eClinical and Qualtrics) will be developed to ensure that guidelines and regulations surrounding the use of computerized systems in clinical trials are upheld.

3.0 DATA AND STATISTICS CENTER RESPONSIBILITIES

The DSC will: 1) develop and apply data management procedures to ensure the collection of accurate and good-quality data, 2) provide source documents and electronic Case Report Forms (eCRFs) for the collection of all data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) prepare instructions for the use of Advantage eClinical and for the completion of eCRFs, 5) conduct ongoing monitoring activities on study data collected from all participating sites, and 6) perform data cleaning activities prior to the final study database lock. Data from mobile surveys, which will be managed by the Lead Node (in REDCap) will be monitored for completeness and quality to the extent possible.

4.0 DATA COLLECTION AND ENTRY

Data will be collected at the study sites on source documents and entered by the site into eCRFs in Advantage eClinical or will be collected via direct entry into the eCRF in Advantage eClinical, or into Qualtrics directly by participants or site staff. If Advantage eClinical is unavailable, the DSC will provide the sites with paper source documents and completion instructions. Data will be entered into Advantage eClinical in accordance with the instructions provided during protocol-specific training and guidelines established by the DSC. Data entry into the eCRFs is performed by authorized individuals. Selected source documents and eCRFs may also require the investigator's signature (wet or electronic). In some situations, data collected on source documents will not be entered into Advantage eClinical, but when it is entered, it will follow the guidelines stated above.

The Principal Investigator at the site is responsible for maintaining accurate, complete and up-to-date research records. In addition, the Principal Investigator is responsible for ensuring the timely completion of eCRFs for each research participant.

5.0 DATA MONITORING, CLEANING AND EDITING

eCRFs will be monitored for completeness and accuracy throughout the study. Dynamic reports listing missing values and forms are available to sites at all times in Advantage eClinical. These reports will be monitored regularly by the DSC. In addition, the DSC will identify inconsistencies within eCRFs and between eCRFs and post queries in Advantage eClinical on a scheduled basis. Sites will resolve data queries by entering all corrections and changes directly into Advantage eClinical or verifying the data are correct as is. Mobile survey data will be monitored for completeness and data quality to the extent possible as these self-reported assessments will be completed remotely by participants.

As described above, the CCC will conduct regular monitoring visits, during which, audits comparing source documents to the data entered on the eCRF will be performed. Any discrepancies identified between the source document and the eCRF will be corrected by the site.

Trial progress and data status reports, which provide information on items such as recruitment, availability of primary outcome, treatment exposure, attendance at long term follow-up visits, regulatory status, and data quality, will be generated daily and posted to a secure website. These reports are available to the site, the Local Node staff, the lead investigative team, the coordinating centers, and NIDA CCTN, to monitor the sites' progress on the study.

6.0 DATA LOCK AND TRANSFER

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DSC. Individual participants and their research data will be identified by a unique study identification number; further, some identifiable data may be collected in eClinical. The study data entry and study management systems used by clinical sites and by DSC staff will be secured and password protected.

At the conclusion of data collection for the study, the DSC will perform final data cleaning activities and will "lock" the study database from further modification. The final analysis dataset will be transferred to the Lead Investigator or designee. De-identified versions of these datasets will also be provided to the NIDA CCTN-designated party for storage and archiving. These datasets will be posted on the NIDA Data Share website.

Reference: http://grants.nih.gov/grants/guide/notice-files/not98-084.html