Peer Intervention to Link Overdose Survivors to Treatment (PILOT): Protocol for a National Institute on Drug Abuse Clinical Trials Network multi-site, randomized controlled trial of peer coaching to reduce overdose risk

Carrie Papa, Erin McClure, Jenna McCauley, Louise Haynes, Timothy Matheson, Richard Jones, Lindsey Jennings, Tricia Lawdahl, Ralph Ward, Kathleen Brady, Kelly Stephenson Barth

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Carrie Papa[1]; Erin McClure[1] PhD; Jenna McCauley[1] PhD; Louise Haynes[1] MSW; Timothy Matheson[2] PhD; Richard Jones[3] MBA; Lindsey Jennings[1] MD; Tricia Lawdahl[4]; Ralph Ward[1] phd; Kathleen Brady[1] MD, PHD; Kelly Stephenson Barth[1] DO

[1]Medical University of South Carolina Charleston US
[2]San Fransisco Department of Public Health San Francisco US
[3]Heritage Health Solutions Coppell US
[4]Faces and Voices of Recovery. -Upstate, SC greenville US

Corresponding Author:
Carrie Papa
Medical University of South Carolina
67 President Street
Charleston
US

Abstract

The increase in opioid-related overdoses has caused a decrease in average life expectancy, highlighting the need for effective interventions to reduce overdose risk. Peer Support Specialists (PSS) offer an appealing strategy to engage overdose survivors and reduce subsequent overdose risk, but randomized controlled trials are needed to evaluate effectiveness. This National Institute on Drug Abuse Clinical Trials Network (NIDA CTN) study is a multi-site, prospective, randomized (1:1) controlled pilot trial (CTN-0107) that aims to evaluate the effectiveness of an Emergency Department (ED)-initiated peer-delivered intervention tailored for opioid overdose survivors (Peer Intervention to Link Overdose survivors to Treatment [PILOT]), compared to treatment as usual (TAU). This study evaluates the effectiveness of the 6-month PILOT intervention compared to TAU on the primary outcome of reducing overdose risk behavior at 6 months post-enrollment. Adults (ages 18+; N=150) with a recent opioid-related overdose are approached in the ED, screened, enrolled and then are asked to complete study visits at months 1, 3, 6 (end of intervention), and 7 (follow-up). Participants randomized to the PILOT intervention receive a 6-month PSS-led intervention that is tailored to each participant's goals to reduce their overdose risk behavior (e.g., overdose harm reduction, housing, medical, and substance use treatment or recovery goals). This paper describes the study protocol and procedures, design and inclusion decisions, and the peer-led PILOT intervention, as well as current study status. Results from this trial will inform ED-initiated PSS-led overdose risk reduction interventions including implementation of PSS services and research in medical settings.

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Carrie E. Papa[1], Erin A. McClure[1,2], Jenna McCauley[1], Louise Haynes[1], Tim Matheson[3], Rich Jones[4], Lindsey Jennings[5], Tricia Lawdahl[6], Ralph Ward[7], Kathleen T. Brady[1], Kelly S. Barth[1]

1. Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, United States
2. Hollings Cancer Center, Medical University of South Carolina, Charleston, SC, United States
3. San Francisco Department of Public Health, San Francisco, CA, United States
4. YouTurn Health, LLC, United States
5. Department of Emergency Medicine, Medical University of South Carolina, Charleston, SC, United States
6. Faces and Voices of Recovery (FAVOR) Greenville, SC, United States
7. Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC, United States

Running Head: PILOT trial to reduce overdose risk behavior

Corresponding Author:
Kelly Barth, DO
Department of Psychiatry & Behavioral Sciences
Medical University of South Carolina
67 President St., MSC 864
Charleston, SC 29425
stephen@musc.edu

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Abstract

The increase in opioid-related overdoses has caused a decrease in average life expectancy, highlighting the need for effective interventions to reduce overdose risk. Peer Support Specialists (PSS) offer an appealing strategy to engage overdose survivors and reduce subsequent overdose risk, but randomized controlled trials are needed to evaluate effectiveness. This National Institute on Drug Abuse Clinical Trials Network (NIDA CTN) study is a multi-site, prospective, randomized (1:1) controlled pilot trial (CTN-0107) that aims to evaluate the effectiveness of an Emergency Department (ED)-initiated peer-delivered intervention tailored for opioid overdose survivors (**P**eer **I**ntervention to **L**ink **O**verdose survivors to **T**reatment [PILOT]), compared to treatment as usual (TAU). This study evaluates the effectiveness of the 6-month PILOT intervention compared to TAU on the primary outcome of reducing overdose risk behavior at 6 months post-enrollment. Adults (ages 18+; N=150) with a recent opioid-related overdose are approached in the ED, screened, enrolled and then are asked to complete study visits at months 1, 3, 6 (end of intervention), and 7 (follow-up). Participants randomized to the PILOT intervention receive a 6-month PSS-led intervention that is tailored to each participant's goals to reduce their overdose risk behavior (e.g., overdose harm reduction, housing, medical, and substance use treatment or recovery goals). This paper describes the study protocol and procedures, design and inclusion decisions, and the peer-led PILOT intervention, as well as current study status. Results from this trial will inform ED-initiated PSS-led overdose risk reduction interventions including implementation of PSS services and research in medical settings.

Keywords: Opioids, overdose, non-fatal overdose involving opioids, peer support specialist, harm reduction, emergency department

Highlights

- Peer support specialists (PSS) offer a strategy to engage overdose survivors.
- Rigorous trials are needed to assess PSS efficacy in reducing overdoses.
- This trial compares a 6-month PSS intervention compared to treatment as usual.
- Results will impact overdose survivor care and engagement.

1.0 Introduction

Increases in overdose deaths globally [1] and in the United States (US) have caused a decrease in average life expectancy [2]. One of the greatest risk factors for a fatal overdose is experiencing a non-fatal overdose involving opioids (NFOO) in the previous year. Indeed, 6-10% of individuals who experience a NFOO die in the following year [3-5]. Survivors of NFOOs most commonly die of another overdose (67%) [3], with the highest risk period being the month following NFOO [5]. Interventions that reduce the risk of a subsequent overdose among NFOO survivors would substantially impact premature mortality.

US Emergency Departments (EDs) treat nearly 140,000 non-fatal overdoses per year [4], providing a point of contact to engage at-risk patients [6, 7]. Although EDs have had some success in implementing certain treatment strategies to reduce overdoses, such as initiating medications for opioid use disorder (MOUD) [8], which decreases mortality among those with opioid use disorder (OUD) [9, 10], NFOO survivors have generally low rates of treatment engagement [3, 11, 12] and low readiness for treatment [13]. Further, substance use disorder (SUD) diagnoses extracted from the medical record show that only 47% of those experiencing a NFOO meet diagnostic criteria for a SUD and only 27% meet criteria for OUD [14]. Taken together, traditional SUD treatment approaches initiated or referred in the ED may have limited success and uptake among an appreciable proportion of NFOO patients who remain at high risk for a subsequent overdose. Strategies are needed to intervene with NFOO survivors in the ED to reduce the risk of subsequent overdoses, regardless of SUD diagnosis or interest and/or readiness for treatment or recovery.

Acknowledging that the NFOO population may be more difficult to engage with traditional medical approaches, work has been focused on developing and evaluating ED interventions that are led by peer recovery coaches with lived experience with substance use that aim to increase treatment engagement. Preliminary results and recent randomized controlled trials characterizing peer interventions have been promising [15-22], though few programs to date have been rigorously evaluated with a generalizable, multi-site sample and with a focus on harm reduction, rather than SUD treatment initiation. One overdose prevention program developed through Faces and Voices of Recovery (FAVOR) in Greenville, South Carolina (SC; FAVOR Overdose Recovery Coaching Evaluation [FORCE]) has shown preliminary success. FORCE is a recovery program led by Peer Support Specialists (PSSs) that trains peers in overdose risk reduction and initiates connection in the ED when an overdose survivor is identified. A recent study evaluated the FORCE model among individuals who were hospitalized [23] and found impressive rates of treatment engagement 6-months post-discharge (84% vs. 34% in the control condition). While that study showed promise for PSS-led recovery coaching, the FORCE intervention has not yet been evaluated among those presenting the ED with a NFOO.

The paper describes a study protocol to evaluate a PSS-led intervention initiated in the ED among NFOO survivors conducted within the National Institute on Drug Abuse Clinical Trials Network (NIDA CTN). This study adapted the PSS-led FORCE model into the Peer Intervention to Link Overdose Survivors

to Treatment (PILOT) and is testing this intervention through a multi-site, randomized, controlled pilot study conducted in three EDs across the US. This paper details the procedures, design, intervention, and implementation of the CTN-0107 Peer Intervention to Link Overdose Survivors to Treatment (PILOT) clinical trial, using SPIRIT reporting guidelines [36].

2.0 Study Design and Procedures

2.1 Study design overview

This 2-arm, multi-site randomized controlled trial evaluates the effectiveness of the 6-month PSS-led PILOT intervention compared with treatment as usual (TAU) initiated in the ED on the frequency of self-reported overdose risk behaviors at six months (end of intervention). This trial (also called PILOT) will enroll 150 patients (ages 18+) who have experienced a recent NFOO from three ED sites in the US. In addition to routine ED care at the time of admission, all ED sites had peer recovery support systems in place in their ED that served as part of TAU.

Participants are approached during their ED admission or shortly after admission (**Figure 1**). If interested, eligible, and enrolled in the study, participants complete research study visits and data collection at Months 1, 3, 6 and 7. Participants randomized to the PSS-led PILOT intervention engage in the PILOT intervention for 6 months (see description below). The primary outcome is a reduction in overdose risk behavior compared between PILOT and TAU participants. Secondary outcomes include engagement in the study and intervention, as well as engagement in recovery and treatment, utilizing a modified SUD Cascade of Care model (Figure 2; detailed description below).

2.2 Study setting

CTN-0107 study sites were selected through a 3-phase process (**Supplemental Figure 1**) to determine appropriateness for inclusion in this trial and ability to recruit NFOO survivors in the ED. The three sites selected for the study are: Prisma Health - Upstate (Greenville, SC), Mercy Health St. Elizabeth Youngstown Hospital (Youngstown, Ohio) and Providence Regional Medical Center Everett (Everett, Washington). All study sites operate under the MUSC policies through a SmartIRB master reliance agreement. This trial is registered with ClinicalTrials.gov (NCT05123027).

2.3 Approach, screening and eligibility

After stabilization as part of routine TAU in the ED, research team members identify and approach patients who may qualify for the study, in-person or remotely (over the phone after ED discharge or if patient leaves against medical advice, but only if permission to contact has been obtained). If the participant is interested in the study and eligible (inclusion/exclusion criteria shown in **Table 1**), informed consent and

screening procedures are performed. Patients could be admitted to the ED for any health issue, substance-related issue, or a NFOO. To be included, patients must meet criterion for a NFOO including: (1) admitted to the ED for any reason and endorse experiencing an NFOO within the past 72 hours or (2) admitted to the ED with any substance-related condition and endorse experiencing a NFOO in the past 30 days. These time frames and reasons for ED admission are meant to be inclusive to allow for non-NFOO reasons for ED admission, while still capturing those with recent NFOO and who are at high risk of subsequent overdoses. This allows for a more generalizable sample of patients in the ED with recent NFOOs, but not necessarily presenting to the ED for a NFOO.

Given the potentially short time that NFOO survivors may be available to research staff in the ED, screening, consent and baseline procedures are allowed to be completed within 1 week after ED discharge. All assessments and procedures conducted during screening, baseline, and during the study are shown in Supplemental Table 1. If patients are not interested in participating in the study or are not eligible, they are offered a brief survey assessing demographics, substance use and overdose history and reasons for not being interested or eligible for the study.

2.4 Randomization

Eligible participants are randomized 1:1 to the PILOT intervention condition or TAU. Participants randomized to TAU receive all standard treatment services provided at the ED, including interaction with TAU PSSs. TAU PSSs (unaffiliated with the study) conduct standard procedures as they would for any NFOO or patient with substance use admitted to the ED, with all sites offering a Screening, Brief Intervention, and Referral to Treatment (SBIRT)-like model. The resources that TAU peers offer within the SBIRT-like model in their ED vary (and are reported through regular surveys), but all sites have the ability to offer naloxone as part of TAU, as required in site selection. TAU interactions are generally contained within one meeting in the ED to provide treatment and harm reduction resources.

For participants randomized to the PILOT intervention, there is an on-call system for the PILOT PSSs such that they are available to come to the ED in-person or remotely to connect with participants. If possible, intervention participants begin the PILOT intervention in the ED. If connection is not made in the ED, the PILOT peer makes attempts to contact the participant as soon as possible after randomization.

Randomization is stratified by study site and unstable housing status (yes/no). A permuted block randomization procedure with random block sizes is used to balance per site and housing status. The randomization schedule uses balanced blocks of varying sizes within strata to ensure lack of predictability along with relative equality of assignment across treatment groups. The randomization procedure is conducted centrally through the CTN Data and Statistics Center (DSC).

2.5 Study visits and retention

During the 7-month study, participants are asked to complete study visits at Months 1, 3, 6 and 7. All

research data is collected by research staff at the study site. PILOT intervention participants engage with their assigned peer during the 6-month intervention. PILOT PSSs do not collect any data for research purposes, which is the responsibility of research coordinators. Assessments completed at study visits are shown in Supplemental Table 1 and all participants receive weekly mobile diaries to complete during the study. To improve retention, study phones are provided to participants, as needed. Retention efforts were pursued throughout the study by PILOT PSSs (for PILOT assigned participants only) and by research coordinators (for both PILOT and TAU participants). If participants were unable to be reached by phone or could not attend study visits at research officies, assertive outreach was used by research staff, that included mailed letters, text messages, visits in the community, and in rare circumstances, home visits with appropriate safety precuations in place, etc. Participants provide locator information for at least two additional contacts if they cannot be directly reached.

3.0 PILOT Intervention Development, Peer Training, and Supervision

3.1 Involvement of people with lived experience

The value of inclusion of people with lived experience in SUD and recovery in developing and delivering this trial is recognized throughout study design, implementation, and dissemination of findings. Two PSSs (RJ, TL) have been integral members of the Lead Research Team and Intervention Team since the inception of the study concept. These individuals bring years of lived experience in SUD recovery as well as supervision of PSSs within recovery-based organizations and have contributed meaningfully to study design, implementation, and dissemination.

3.2 PILOT intervention development and components

The PILOT intervention was adapted from the FORCE program, which used certified PSSs trained in engaging overdose survivors presenting to the ED. The CTN-0107 Lead Intervention Team, including FORCE PSSs (RJ and TL), adapted the FORCE intervention (developed and implemented by RJ) and developed the PILOT intervention manual for the current trial. The process of manual development included a literature search to complement what was learned from the FORCE implementation and an iterative process involving all members of the Intervention Team to identify the Key Principles of the intervention. The underlying philosophy of the intervention is grounded in a combination of motivational interviewing, case-management, health coaching, and Assertive Community Engagement. The PILOT Intervention Manual was reviewed by an independent PSS, and feedback was incorporated before study enrollment began. The PILOT Intervention Manual was considered a “living document” to be further molded and adapted by the PSSs trained on the study.

The PILOT Intervention Manual describes three Key Principles: 1. *Assertive Engagement, 2. Participant-Directed* Care, and 3. *Effective Supervision*. *Assertive Engagement* refers to the relationship between the PILOT PSS and the participant, as well as the expectation of active engagement with community partners. Characteristics of *Assertive Engagement* include: 1) connection with and support of the participant informed by the PSSs lived experience, 2) the PSS taking responsibility for maintaining connection, 3) comprehensive knowledge of community resources, 4) linkage to services, 5) integration of family and other social supports, and 6) effective utilization of overdose harm reduction techniques.

The principle of *Participant-Directed* Care in the PILOT intervention refers to the inclusion of participant-defined goals. Training on this approach, grounded in Motivational Interviewing (MI) [24], was provided to PSSs during peer national training (described below), and is reinforced during regular supervision sessions. The PSS assumes responsibility for follow-up after ED discharge and continued engagement and contact throughout the intervention. By keeping in contact with participants over time and utilizing motivational interviewing approaches, PSSs are available to individuals regardless of their level of interest in or readiness for treatment. Engagement with the individual is based on their needs, which may evolve during the intervention.

Effective Supervision was initiated from the time of PSS hire and continues during study enrollment. At the study site level, supervision is conducted by a Lead PSS, who is the on-site PILOT peer supervisor and provides at least weekly supervision. At the national level, a weekly, virtual supervision call for all PSSs is led by the Intervention Team, which includes a doctorate-level psychologist, a master's level social worker, and two experienced PSSs. All PSS supervision sessions include informal discussion of participant cases, facilitated sharing of work-related experiences with feedback and support, and formal case presentations. National supervision also includes brief didactic and experiential review of key principles, including real-time practice of MI, promotion of self-care, awareness of safety in the field, and implementation of practical, participant-directed, and strengths-based case management.

3.3 PSS training

All PILOT PSSs were required to hold a nationally recognized Certified Peer Support Specialist (CPSS) certificate (or equivalent based on the state). PILOT PSSs participated in the virtual all-study National Training led by the National Intervention Team and were required to complete all Human Subjects Protections and Good Clinical Practice training. The PSS training provided didactic and experiential (role-play) training using the PILOT intervention manual, including discussion of PILOT PSS roles, responsibilities, and boundaries; detailed overviews of each treatment group; appropriate MI-based techniques and role-plays; and importance of active supervision. During the National Training, training on the MI approach was provided, and role-plays were conducted in groups of 2 PSSs with feedback provided by the Intervention Team. Post-National Training is delivered via conference calls, webinars, and written materials. Competence in basic MI

is reinforced through a taped recording of a mock participant session or a real time roleplay over Zoom, which is reviewed by the Intervention Team.

3.4 Peer documentation and fidelity

Given the interactions between a PSS and an individual are fluid, responsive to changing needs, and often spontaneous, the Intervention Team worked with the Lead Team PSSs to develop a checklist of the most common activities utilized (e.g., outreach, engagement, discussion of lived experience, connection to resources, naloxone distribution, identification of participant-directed goals). These activities are captured in the Peer Intervention Log (PIL) that the PILOT PSSs fill out daily, describing the activities they utilized with a participant. PILs are completed, even if no contact or intervention had been delivered on that day.

Based on feedback from the Lead Team PSSs, direct fidelity measurement (e.g., recorded PSS-participant interactions) was found to be infeasible since this could inhibit spontaneity and rapport-building. Instead, metrics of peer activity, content, frequency, etc. are collected during the 6-month intervention in the PIL. Additionally, local and national supervisors perform fidelity assessments via case presentations during weekly supervision at the local level and during formal case presentations delivered by each PSS during national supervision.

4.0 Measures and Assessments

4.1 Primary outcome

The primary outcome measure is a modified and expanded version of the Opioid Risk Behavior Checklist (ORBC), adapted from Bohnert et al. (2016) [25]. The modified ORBC (**Supplemental Figure 2**) was adapted from similar questionnaires to capture overdose risk behaviors in this or similar populations [17, 25, 26] (RELAY RCT; NCT04317053), and developed based on known factors associated with risk for overdose [25, 27-32]. The PILOT ORBC is a 13-item scale, with 11 of the items used to generate a total risk score (ranging from 0-44); higher scores indicate greater frequency and number of overdose risk behaviors.

4.2 Secondary outcomes

The secondary outcomes of the study are: 1) number of steps achieved on a modified SUD Cascade of Care at 6 months after ED admission (**Figure 2**); and 2) engagement with the study and PILOT intervention, measured by (a) the number of potentially eligible patients *approached* in the ED compared with the number willing to be enrolled in study procedures and (b) the length of enrollment in the trial among those randomized to PILOT (defined as the time from baseline to last meeting with the PILOT PSS). The SUD Cascade of Care was developed by the CTN-0107 Lead Team, informed by published work documenting an

OUD Cascade of Care [33], to capture improvements that may otherwise be missed through existing assessments meant for those with SUDs or greater severity of substance use. The Cascade of Care outlines 10 steps representing different stages of SUD treatment or recovery engagement ranging from harm reduction to engagement in formal SUD treatment or MOUD. Participants do not need to meet criteria for an SUD or OUD to be included in steps achieved, which also includes steps towards overdose harm reduction and recovery capital. To assess steps achieved on the SUD Cascade of Care, participants are asked to complete an assessment battery which includes a study-developed Harm Reduction Checklist (HRC), a Steps Achieved Assessment Form (SAF), MOUD Confirmation Assessment, a DSM-5 Checklist for Substance Use Disorders [34], a Urine Drug Test (UDT), and the Assessment of Recovery Capital (ARC) Scale [35] (Supplemental Figure 2 for locally developed assessments). All enrolled participants are considered to have 0 steps achieved at the time of the baseline visit, even if they are engaging in treatment or recovery services at the time of enrollment/baseline, with a maximum of 10 steps possible to be achieved by the end of treatment visit (Month 6).

4.3 Safety

The NFOO population is at high risk of adverse events and subsequent overdoses, and this study conducts targeted safety monitoring. Targeted safety monitoring events include participant death, overdoses, ED visits, and hospitalizations. Assessment for suicidality is screened for and handled according to approved safety procedures at all study visits. In addition, study staff safety protocols for community visits were developed when conducting in-person visits in the community. Safety and data oversight is provided by the NIDA CTN and Emmes Clinical Coordinating Center, site-level IRBs and the MUSC IRB, as well as a Data Safety Monitoring Board that meets annually.

5.0 Statistical Analysis Plan

5.1 Primary outcome analyses

The primary outcome is the effectiveness of PILOT (compared with TAU) as measured by the past month total score of the self-report ORBC assessment at Month 6 (end of intervention). The study hypothesis is that PILOT intervention participants will have a lower ORBC total score at Month 6 (i.e., lower frequency of self-reported overdose risk behaviors) compared to TAU participants. The primary outcome of ORBC total score at Month 6 will be analyzed with a longitudinal mixed effect Poisson regression model incorporating total score at earlier time points. Fixed effect covariates include baseline ORBC total score, treatment assignment, days in the study (time since randomization), site, stratum, and an interaction between treatment and days. Days will be treated as a categorical variable. A random effect will be included to account for repeated measures per participant. The treatment effect will be given as a rate ratio (RR; as the exponential of

group and days interaction at Month 6 plus the main effect of randomized group) along 2-sided p-values and 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 Month 6, while all other variables are the same.

5.2 Secondary outcome analyses

For the number of steps achieved along a modified SUD Cascade of Care, analysis will be similar to that for primary outcome, with 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. A RR with 95% confidence interval and p-value will be reported. Participants entering the trial may not have a primary diagnosis of OUD, or any SUD. Because of this, some steps may not be eligible at baseline. If, during the study, the participant endorses OUD or other SUD, they will become eligible for these steps. Alternatively, with the increasing co-use and contamination of methamphetamine with fentanyl, people with primary methamphetamine use disorder (and no diagnosis of OUD) may be placed on MOUD, and this study will measure that within this population.

Other secondary outcomes (i.e., the number of participants approached and number who were willing to engage with PILOT peers, and percent of those approached who were willing to engage) will be reported by summary statistics with 95% confidence intervals. The length of engagement with PILOT will be similarly summarized.

5.3 Power analysis and sample size estimation

Power analyses and sample size calculation were based on the primary outcome of comparing ORBC total score differences at Month 6 between PILOT and TAU participants. The self-reported overdose risk behaviors to be used for this trial are modified and expanded from a version used by Bohnert et al (2016) in which the maximum score was 32, with average baseline scores of 3.3 and 3.8 in their control and intervention groups, respectively [25]. They used a Poisson regression model to estimate the intervention effect, reported to be 0.72 rate ratio (RR). For the power simulations conducted for this study, a baseline mean score of 3.55 was used, with a treatment effect of 0.72. With a mean of 3.55 at baseline and a RR of 0.72, there is over 90% power to detect the expected treatment effect with a total sample size of 150.

6.0 Study Design Decisions

Several key decisions were made regarding the most appropriate sample for this study. The study enrolled ED patients who had experienced a recent NFOO, though a diagnosis for OUD or SUD was not required for inclusion. Since a previous study reported only 47% of NFOO patients had a known diagnosis of

SUD and 27% had an OUD diagnosis as documented in the medical record [14], individuals were included regardless of SUD or OUD status given increased risk of subsequent overdoses and the potential to be overlooked as part of established services in the ED. Given that study outcomes are based on opioid overdose risk behavior and secondarily on an SUD continuum of care, heterogeneity in opioid use and SUD diagnosis among the sample increases generalizability of study findings.

Some individuals admitted to the ED after a NFOO may not know they have experienced an overdose involving opioids. Additionally, many individuals experience NFOOs and do not seek medical attention, even after naloxone is administered. The study considers an individual to have experienced a NFOO if they self-report affirmatively that they believe they experienced an overdose and that the overdose may have involved opioids. This decision increased inclusivity, acknowledging that high risk overdose events happen commonly without formal medical attention and/or naloxone reversal. If an individual denied having an overdose, even if they were given a reversal agent and/or it was medically assessed to be a NFOO, they were not eligible for inclusion, given the PILOT intervention specifically focuses on overdose risk behaviors.

7.0 Current Study Status and Impact

Enrollment of study participants commenced in December 2021 and concluded in June 2023, with a final sample of 150 participants being enrolled into study procedures and randomized. Final follow-up visits occured through February 2024. The overall goal of this study is to provide data on the effectiveness of a PSS-led intervention for NFOO survivors presenting to ED settings to reduce overdose risk behavior at 6 months following ED admission. To date, the study has developed and delivered a PSS intervention within a research model and completed enrollment, demonstrating the feasibility of both completing a multi-site trial in this area and recruiting the target population. Outcomes of this trial will contribute important information to the field, including: 1) a detailed description of the characteristics and 6-month course of NFOO survivors presenting to three geographically different ED settings between December 2021 and June 2023, 2) a description of the nature, content, and dosing of a research-delivered PSS intervention, and 3) lessons learned in the research implementation of an ED-initiated PSS intervention. Study results will contribute much-needed, rigorous, randomized, controlled data to the growing field of research and interventions to address overdoses and reduce risk for subsequent overdoses among a generalizable sample of NFOO survivors.

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