Title: Teaching Health promotion and Resilience in Varied Environments: a peer-led intervention following hospital discharge

Grant Number: 1R01DA057633-01

Funded by: National Institutes of Health (NIH) National Institute for Drug Abuse (NIDA)

NCT Identified Number: NCT06843213

IRB #: 23120016

Version Date: 27 July 2026

Protocol Version Number: v. 2.0

Abbreviated Title: THRIVE Study

Principal Investigator:	J. Deanna Wilson, MD, MPH University of Pennsylvania 51 North 39th Street Mutch Building, Family Medicine 7th floor Philadelphia, PA 19104 Phone: 610-618-0932 E-mail: jacqueline.wilson1@pennmedicine.upenn.edu
DCC/Statistical Design PI:	Cristina Murray-Krezan, PhD University of Pittsburgh Center for Biostatistics & Qualitative Methodology 200 Meyran Ave, Suite 200 Pittsburgh, PA 15213
Site PI:	Jane Liebschutz, MD, MPH University of Pittsburgh Center for Research on Health Care 3609 Forbes Ave, 2nd Floor Pittsburgh, PA 15213

TABLE OF CONTENTS

STATEMENT OF COMPLIANCE 5
PROTOCOL SUMMARY 6
1 Schema 8
2 Schedule of Activities (SOA) 9
INTRODUCTION 12
3 Study Rationale 12
4 Background 12
5 Risk/Benefit Assessment 15
5.1.1 Known Potential Risks 15
5.1.2 Known Potential Benefits 16
OBJECTIVES AND ENDPOINTS 16
STUDY DESIGN 18
6 Overall Design 18
7 Scientific Rationale for Study Design 18
8 Justification for Intervention 19
9 End-Of-Study Definition 19
STUDY POPULATION 19
10 Inclusion Criteria 20
10.1.1 Patients 20
10.1.2 Providers 20
11 Exclusion Criteria 20
11.1.1 Patients 20
11.1.2 Providers 20
12 Involvement of Vulnerable Participants 20
13 Involvement of Pregnant Participants, babies in utero, or neonates 21
14 Lifestyle Considerations 21
15 Screen Failures 21
16 Strategies for Recruitment and Retention 21
16.1.1 Costs 22
16.1.2 Compensation 22
17 Study Interventions(s) or Experimental Manipulations(s) Administration 22

17.1.1 Study Intervention or Experimental Manipulation Description 22
17.1.2 Administration 22
18 Fidelity 23
18.1.1 Interventionist Training and Tracking 23
19 Concomitant Therapy 25
20 Rescue Therapy 25
STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 25
21 Discontinuation of Study Intervention/Experimental Manipulation 25
22 Participant Discontinuation/Withdrawal from the Study 25
23 Lost to Follow-up 26
STUDY ASSESSMENTS AND PROCEDURES 26
24 Screening Procedures 26
24.1.1 Screening activities performed prior to obtaining informed consent 26
24.1.2 Screening activities performed after a verbal consent for screening has been obtained 26
25 Study Evaluations & Procedures 26
25.1.1 Biospecimen Evaluations 27
25.1.2 Samples for Genetic/Genomic Analysis 27
26 Safety Assessments 27
Adverse Events and Serious Adverse Events 28
26.1.1 Definition of Adverse Events (AEs) 28
26.1.2 Definition of Serious Adverse Events (SAE) 28
26.1.3 Classification of an Adverse Event 29
26.1.4 Time Period and Frequency for Event Assessment and Follow-Up 30
26.1.5 Adverse Event Reporting 30
26.1.6 Serious Adverse Event Reporting 30
26.1.7 Events of Special Interest 31
26.1.8 Reporting of Pregnancy 31
27 Unanticipated Problems 31
27.1.1 Definition of Unanticipated Problems (UP) 31
27.1.2 Unanticipated Problem Reporting 31
STATISTICAL CONSIDERATIONS 31

28 Statistical Hypothesis 31
28.1.1 Primary Hypothesis 31
28.1.2 Secondary Hypotheses 32
28.1.3 Exploratory Hypotheses 32
29 Sample Size Determination 32
29.1.1 Original Sample Size Justification 32
29.1.2 Updated Sample Size Justification 33
30 Populations for Analyses 33
31 Statistical Analyses 34
31.1.1 General Approach 34
31.1.2 Analysis of the Primary Endpoints 34
31.1.3 Analysis of the Secondary Endpoint(s) 34
31.1.4 Safety Analyses 34
31.1.5 Baseline Descriptive Statistics 35
31.1.6 Planned Interim Analyses 35
31.1.7 Exploratory Analyses 35
31.1.8 Missing Data 36
REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS 36
32 Informed Consent Process 36
32.1.1 Consent/Assent Procedures and Documentation. 36
32.1.2 Consent of Participants who are, or become, decisionally impaired 36
33 Study Discontinuation and Closure 36
34 Confidentiality and Privacy 37
34.1.1 Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies 37
34.1.2 Certificate of Confidentiality 38
35 Future use of Stored Specimens and Data 38
36 Safety Oversight 38
37 Clinical Monitoring 39
38 Quality Assurance and Quality Control 39
39 Data Handling and Record Keeping 40
39.1.1 Data Collection and Management Responsibilities 40

40 Protocol Deviations and Non-Compliance 41

41 Human Data Sharing, including Genomic Data Sharing, and Publication 41

41.1.1 NIH Data Management and Sharing Policy and NIH Genomic Data Sharing Policy Compliance 41

41.1.2 NIH Public Access Policy Compliance 41

42 Conflict of Interest Policy 42

ABBREVIATIONS 42

REFERENCES 44

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent scripts and/or form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

PROTOCOL SUMMARY

This is a pragmatic, hybrid type I effectiveness/implementation randomized controlled trial (RCT) comparing the Teaching Health promotion and Resilience in Varied Environments (THRIVE) peer-led intervention model to enhanced usual care (EUC). For this phase III RCT, at least N=262 participants from three practice settings will be randomized one-to-one to the THRIVE model or EUC. The purpose of the study is to develop an acceptable, feasible, and effective peer-led bundle of health promotion strategies. The THRIVE model, which includes an in-person session boosted by text messages, will build on effective models utilizing people with lived experience (PWLE) to engage people who use drugs (PWUD), deliver knowledge and skills, and enhance motivation.

Synopsis

Title:	THRIVE: Teaching Health promotion and Resilience in Varied Environments: a peer-led intervention following hospital discharge
Study Description:	We will conduct a 2-arm 1:1 randomized controlled trial of the effectiveness of the Teaching Health promotion and Resilience in Varied Environments (THRIVE) peer-led model compared to enhanced usual care. We will randomize at least 262 participants with 131 randomized to the THRIVE model and 131 to the enhanced usual care control arm (see Figure 1), allowing for 25% attrition at 6 months. Our hypotheses are that individuals receiving the THRIVE intervention will have a reduced self-reported NFOD or SSTI compared to controls receiving enhanced usual care at 6 months, and because of adaptation, there will be minimal heterogeneity of treatment effect by specific sub-population.
Objectives:	**Primary Objective:** To assess the efficacy of the THRIVE intervention in reducing the cumulative incidence of self-reported non-fatal overdose or skin and soft tissue infection between hospital discharge (baseline) and six months post-discharge, compared to usual care, using a hybrid type 1 randomized controlled trial design.
	Secondary Objectives: To assess the effectiveness of the THRIVE intervention compared to EUC at lowering the incidence of the independent outcomes of: (1) non-fatal overdoses (2) skin and soft tissue infections We will assess challenges and facilitators to implementation of the THRIVE intervention.
Endpoints:	Primary Endpoint: The cumulative incidence (incidence proportion) of the composite measure of: (1) at least one self-reported episode of non-fatal overdose (NFOD) between baseline and six months, OR (2) at least one self-reported episode of skin or soft tissue infection (SSTI) between baseline and six months.
	Secondary Endpoints: 1) The cumulative incidence of NFOD from baseline to 6 months 2) The cumulative incidence of SSTI from baseline to 6 months
Study Population	We will recruit at least 262 patients who are 18 or older on the day of admission, who are English-speaking and- reading, and who meet DSM-5 criteria for having an opioid use disorder.

Description of Sites/Facilities Enrolling Participants	Participants will be recruited from UPMC Presbyterian-Montefiore and UPMC Mercy inpatient and emergency department setting, and UPMC Shadyside inpatient setting.
Description of Study Intervention:	Participants in the intervention group will receive a 60-minute, face-to-face intervention delivered by a person with lived experience (PWLE). The intervention will include referrals to health promotion resources, education on healthy behaviors, and access to health promotion supplies. They will conclude with goal setting around a participant-identified health behavior(s). They will then receive weekly text messages (for 12 weeks) from the PWLE checking on their goal setting, providing feedback, and helping create a plan for addressing likely challenges.
Study Duration:	36 months
Participant Duration:	6 months

1 SCHEMA

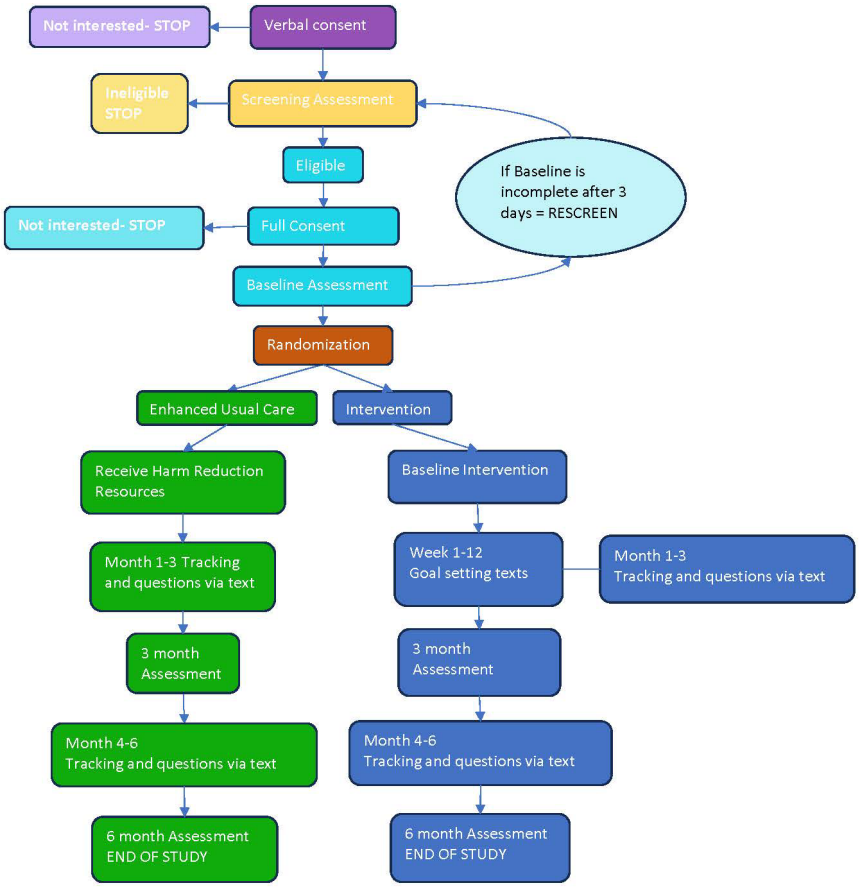


Figure 1. Study Schema

2 SCHEDULE OF ACTIVITIES (SOA)

Table 1. Research Assistant Schedule of Activities

Activities	Pre-screening (Pre-consent)	Baseline	Week 4** Day 26+5	Week 8 Day 54+5	Week 12 Day 82+5	Week 12 Day 84 + 14	Week 16 Day 110 +5	Week 20 Day 138 + 5	Week 24 Day 166 +5	Week24 Day 168 +14
Provider Referral	X	-	-	-	-	-	-	-	-	-
Eligibility Screen	X	-	-	-	-	-	-	-	-	-
Informed Consent	-	X	-	-	-	-	-	-	-	-
Alternative Contacts	-	X	-	-	-	-	-	-	-	-
Telephone Tracking Form (if applicable)	-	X	-	-	-	-	-	-	-	-
Baseline Assessment	-	X	-	-	-	-	-	-	-	-
Randomization	-	X	-	-	-	-	-	-	-	-
Control Group Education Materials (if applicable)		X								

Peer Support Specialist Referral	-	X	-	-	-	-	-	-	-	-
Compensation Tracking Form	-	X	-	-	-	X	-	-	-	X
Assessment Tracking Form	-	X	X	X	X	X	X	X	X	X
Outcome Evaluation										
Texting Assessment	-	-	X	X	X	-	X	X	X	-
Telephone Assessment	-	-	-	-	-	X	-	-	-	X
Adverse Events Reporting	-	X	X	X	X	X	X	X	X	X

**** Day 1 is defined as the day of actual discharge from the hospital setting or emergency department.**

Table 2: Peer Support Specialist Schedule of Activities

Intervention Procedures	Baseline to Discharge + 3 days	Week 1 Day 7 +/- 3 days	Week 2 Day14 +/- 3 days	Week 2 Day 21 +/- 3 days	Week 3 Day 28 +/- 3 days	Week 4 Day 35 +/- 3 days	Week 5 Day 42 +/- 3 days	Week 6 Day 49 +/- 3 days	Week 7 Day 56 +/- 3 days	Week 8 Day 63 +/- 3 days	Week 9 Day 70 +/- 3 days	Week 10 Day 77 +/- 3 days	Week 11 Day 84 +/- 3 days
Face-to-Face Intervention	X	-	-	-	-	-	-	-	-	-	-	-	-
Weekly Text Messages	-	X	X	X	X	X	X	X	X	X	X	X	X
Intervention Tracking Form	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events Reporting	X	X	X	X	X	X	X	X	X	X	X	X	X

**** Day 1 is defined as the day of actual discharge from the hospital setting or emergency department.**

INTRODUCTION

3 STUDY RATIONALE

Health promotion services and strategies are innovative tools. Health promotion is defined as a set of practical strategies and services focused on reducing negative consequences associated with stigmatized behaviors[1] such as injection drug use (IDU). Health promotion strategies are pragmatic and delivered in ways that are non-judgmental, compassionate, and promote healthier behaviors based on "where people are."[2–5] Health promotion includes *education on safer injection practices* and ways to reduce infectious risks, which our own work has shown reduces risky injection behaviors.[6,7] There is high-quality data showing that *overdose education and take-home naloxone* programs can reduce fatal overdose when implemented in community settings,[8] and when naloxone is prescribed in clinical settings.[9] Although the evidence is less robust (with smaller sample sizes and less rigorous experimental designs), using *fentanyl test strips* is feasible, acceptable, and leads to more accurate perceptions of overdose risk and subsequent behavioral changes.[10–13] There are significant knowledge gaps on how best to deliver these health promotion services equitably.

4 BACKGROUND

Clinical integration of health promotion services is an often-missed opportunity. While health promotion services have typically been offered in public settings, often by community-based organizations or public health agencies, uptake of health promotion services remains poor.[14] Integrating health promotion services into clinical settings would enable more distribution of information and resources, would take advantage of the frequent contact people who use drugs (PWUD) have with the healthcare system, and may help bypass some of the stigma associated with accessing safe syringe programs (SSPs).[15] However, challenges to doing so exist: our studies show that while clinicians were willing to offer education on overdose prevention and naloxone, they failed to do so because of time constraints, personal beliefs, and low self-efficacy in prescribing and counseling.[16–18] A national survey showed that less than one percent of clinicians had ever prescribed syringes to PWUD, few talked to patients they knew used drugs about their use, and most had significant knowledge gaps related to doing both.[19] Recognizing the challenges of having clinicians deliver health promotion education, we conceptualized a person with lived experience (PWLE) as the delivery mechanism for health promotion education in the clinical setting.

Peer recovery support is an effective delivery mechanism. There is a robust body of literature describing the integration of PWLE in health promotion services[20,21] in ways that can increase feasibility, acceptability, and quality of services provided to PWUD.[22] PWLE are able to draw explicitly on their own experiences to facilitate trust-building, support engagement, and increase credibility.[21,23] They help minimize enacted stigma, create safe environments with less differentials in power,[24,25] and improve outreach to populations unlikely to be reached through other mechanisms.[26,27] In addition to their role in relationship-building, studies describe PWLE as effective in multiple roles including the direct provision of health promotion supplies,[27,28] through delivery of education on overdose prevention and naloxone use,[29] through instruction on safer injection,[30,31] and in counseling to reduce risk of HIV.[32] Additionally, studies show PWLE are more effective at transferring knowledge[33] to PWUD. While studies highlight the benefits of PWLE in community-based health promotion, their traditional role in clinical settings has focused on treatment engagement.

The <u>rigor of prior research</u> includes strong evidence demonstrating efficacy of health promotion in reducing opioid-related mortality, and in showing the benefits of engaging PWLE in both the research design process and in the delivery of health promotion services. Because current research demonstrates poor delivery of health promotion services across sub-populations, we will tailor the THRIVE intervention

for various groups, and will guide an implementation strategy that prioritizes widespread adoption of the model. Additionally, as the THRIVE model was co-created with PWLE and will be further tailored using human-centered design approaches that incorporate the perspectives of PWUD, we anticipate greater likelihood of success as community-partnered research has been shown to lead to recruitment of various participants, improved study retention,[35–37] and greater likelihood of research leading to changes in policy and practice.[38–40]

Clinician barriers to integrating health promotion education into clinical settings: We surveyed 148 clinicians who treat both adolescent and adult patients, and documented an action gap with frequent exposure to patients with opioid use disorder (OUD), but few offerings of health promotion services including naloxone.[16,17] In response to these gaps, we created low-literacy, patient education materials and trained clinicians to give an office-based brief intervention (lasting 5 minutes) offering overdose education and naloxone. **The brief intervention materials will form the basis of the overdose education component of the THRIVE intervention.**

Brief skin and needle hygiene intervention delivered to hospitalized PWUD: We conducted a randomized controlled trial (n=252) comparing usual care to receipt of a brief skin and needle hygiene intervention (SKIN).[6,7] Outcomes included total emergency department (ED) and hospital visits, injection drug use (IDU)-related ED visits and hospitalizations, skin and soft tissue infections (SSTIs), injection frequency, and skin cleaning practices, which were gleaned from 12-month self-report and electronic health record (EHR) review. At study conclusion, the SKIN intervention significantly reduced IDU-related ED visits and uncleaned skin injections. Intervention participants experienced fewer total injection episodes and 35% fewer SSTIs over the year compared to controls, however differences were not statistically significant. **SKIN will serve as basis for the safe injection component of the THRIVE bundle. As SKIN showed low adherence to two face-to-face sessions, we modified THRIVE to include one face-to-face session followed by text messages and booster session content pushed to the participant's phone.**

Hospitalized patients with complications from IDU have high morbidity and mortality post-discharge (manuscript under review): In a retrospective cohort study using EHR data from the study health system, we characterized a population of 8313 individuals hospitalized with skin, soft tissue, and other bacterial infections from IDU. We examined recorded outcomes at 30, 90, and 365 days. Within one year of hospital discharge, 12.8% died with 61% of deaths occurring within 90 days of discharge. We identified persistent differences in delivery of medications to treat OUD with lower receipt among specific sub-populations even after adjusting for other variables. **The findings demonstrate the feasibility of following patients prospectively through EHR to corroborate self-reported findings. As the first 90 days post-discharge is characterized by 60% of the deaths and 40% of the overdoses, we will deliver the THRIVE intervention during this high-risk time period.**

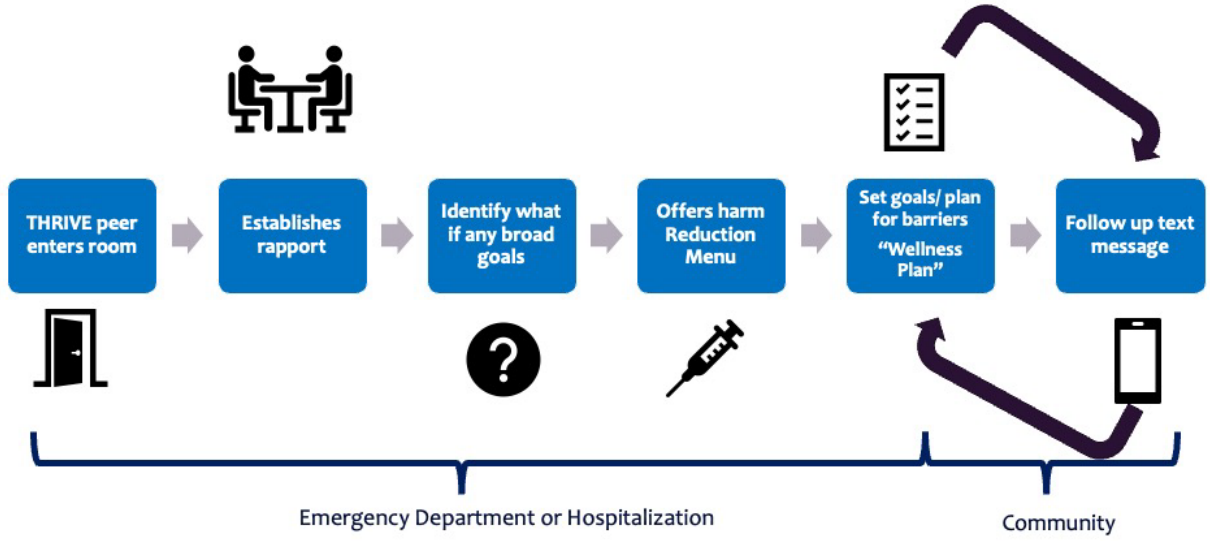
Hospital-based intervention using PWLE reduces morbidity and mortality among people with OUD: We conducted a retrospective, propensity-score matched case-control study of a hospital-based intervention using PWLE as part of the addiction medicine consult service (AMCS).[38] We compared propensity-score matched control participants (n=2172) to an AMCS intervention group (n=711). The AMCS intervention included PWLE who engaged patients during acute hospitalization. While the intervention itself was free-form and focused on engaging patients in motivational interviewing, offering withdrawal management, and facilitating linkage to outpatient hospital discharge, the outcomes showed a 2.35% absolute reduction in mortality at 90 days compared to control, and a 2.15% reduction in 7-day hospital readmission rate. **This demonstrates the feasibility of training and integrating PWLE in the hospital setting as part of a broader hospital-based intervention, which is a critical component of the THRIVE model.**

The initial proposed THRIVE model draws on components selected from constructs derived from the Capacity-Opportunity-Motivation- Behavior (COM-B) model and Theoretical Domains Framework (TDF),[39–41] with a focus on improving knowledge and skills (capability); altering social influences and

environmental contexts to access health promotion services (opportunity); and changing beliefs about the consequences of drug use, self-efficacy in using health promotion strategies, feelings about social self-descriptors, and emotions (motivation).

In order to further design the THRIVE intervention components, we relied on a Design Sprint process to co-create the intervention with "end-users," in this case PWUD. The Design Sprint process was developed by Google Ventures[35,36] and allows for rapid design and testing of models co-created with end-users. Our Design Sprint was adapted to include four two-hour long sessions with a total of 14 PWLE (defined as current or historical use of drugs). Through a series of human-centered design exercises, they co-created the THRIVE intervention to best reflect the needs of PWUD.

Figure 2. THRIVE Model



The THRIVE model includes a THRIVE peer support specialist (a PWLE) who meets study participants as early as possible during their hospital stay (either in the ED or inpatient room). The initial meetings will occur face-to-face in the hospital setting. They will focus on establishing rapport through a semi-structured approach that encourages them to leverage their lived experience and shared experiences to build rapport. They will then identify what, if any, broad goals the study participant may have with respect to health or substance use, and will then offer a health promotion menu that provides education on core topics such as overdose prevention, including naloxone; wound care, including information on xylazine wounds; safer consumption (smoking and injecting), medications to treat OUD, drug testing, preventing HIV, booty bumping, coping with stress, and ways to link to care. Participants will be offered information on specific topics of their choice and will be taught using a mixture of multimedia, in-person demonstrations, and teach-back. They will then help participants create specific goals for after discharge from the acute care setting that are focused broadly on wellness. These may be related to specific topics, like cleaning skin to avoid infectious complications, or could be broader and focused on tasks like making a primary care appointment. The THRIVE peer support specialist will also help participants brainstorm what, if any, challenges are present that may prevent them from meeting their goals, and will help develop a plan to overcome or minimize possible challenges. The goals, challenges, and plans to address potential challenges will serve as an individualized "Wellness Plan" that will then be given to the participant. The THRIVE peer support specialist will then follow up via weekly text message over 12 weeks to check on the participant's progress, revise or create new goals, and revise or update the Wellness Plan.

5 RISK/BENEFIT ASSESSMENT

5.1.1 Known Potential Risks

All study staff will have received appropriate regulatory and ethical training as part of the requirements for the Pitt IRB. Overall, potential risks associated with participation in the study are unlikely and low for both patients and providers. There is little physical risk for either group. There will be potential for psychological risks to patients in this study due to the nature of personal questions asked. Information collected from patient participants will be confidential. Information collected from provider participants will be anonymous.

Patients: Patients will be asked about recent substance use, medical conditions, and other health-related information as part of a structured interview. They may be upset about these questions or feel triggered to use substances. As disclosed below, we will be using a variety of safeguards to reduce these risks. Additionally, they may experience discomfort or boredom when completing the initial baseline survey instrument or the follow-up interviews. Peers will be texting participants in the intervention group weekly to deliver content related to health promotion and goal-setting. These weekly messages may lead participants to be triggered to use substances or could cause mental distress. Because information will be sent via text message, there is possible risk for inadvertent disclosure of substance use to others. All study patient participants will receive automated monthly text messages asking about recent substance use and health conditions. There is a risk the monthly automated text messages could be intercepted leading to possible disclosure of substance use to others. Risk mitigation measures are described below.

Participants will be at-risk for potential breach of confidentiality. All measures will be taken by study staff to ensure patients' confidentiality is maintained. Information will be collected using encrypted text messaging platforms. Prior to study start, participants will be educated on ways to secure text messages on their mobile device. In addition, the initial weekly text message during each weekly intervention encounter will not include any sensitive information asking about substance use or behaviors, and will not refer to participants by first name to help avoid accidental disclosure. Study intervention staff will use special work phones that are password protected and will only be used for research purposes. Audio recordings of intervention sessions will be captured for fidelity monitoring purposes. Though the recordings will be anonymous, participants may share sensitive or identifiable information during the intervention session, which could put the participant at risk for a breach of confidentiality in the event that the audio recording device is lost or stolen. To mitigate this risk, research staff will keep the audio recording device with them at all times when in use and store the device in a locked drawer or cabinet in a secure location when not in use. Audio recordings will be uploaded to an encrypted location to be shared with the investigator for review and will be destroyed immediately once reviewed. There is also a potential legal risk, as we are asking about information that may identify individuals as engaging in illegal behaviors, such as IDU, although we will obtain a Certificate of Confidentiality to provide additional legal protections.

Study assessment staff, who will be conducting the assessments with participants, will confirm participants' willingness to complete the assessments prior to starting. They will offer frequent breaks if desired and can complete the survey assessments in multiple visits if desired by the participant. They have been trained to respond to patients who may feel strong emotions. If participants desire assistance with accessing services, the study assessment staff will facilitate a warm hand-off to the Project Coordinator to link them to the appropriate clinical or health promotion resources.

Study intervention staff are peers, or PWLE. They are trained as certified peer recovery specialists to support individuals who use substances. They will be responsible for delivering the initial THRIVE intervention face-to-face and then will send weekly text messages to follow-up on participant goals identified during the previous week. They have received specific training, as part of the certified peer recovery specialist training, to de-escalate patients, use motivational interviewing strategies to reduce

resistance and strong emotions, and support patients broadly. In order to minimize boredom or frustration, they will confirm prior to each interaction that participants still wish to remain in the study and participate.

We will include regular monitoring of participant responses and emotional well-being with the study team. We will continue ongoing training for research staff on how to respond to emotional responses from participants and how to offer compassionate, non-judgmental information and referrals if requested. Staff will be trained to immediately report any Adverse Events (AEs) and/or participant distress.

Providers: We will survey providers at the conclusion of the trial period. Providers will receive an electronic survey link to complete. Provider participants may feel uncomfortable about answering these questions or may experience boredom. We are collecting information anonymously, and there are minimal harms associated with the electronic survey as responses are not able to be identified.

5.1.2 Known Potential Benefits

Benefits may accrue to patients and providers because the THRIVE intervention may ultimately lead to improved delivery of services to treat patients with similar conditions. Patients will receive access to health promotion education and resources that may allow them to reduce their risk for significant opioid-related morbidity and mortality. Risks to individual participants are modest and reasonable in light of the potential benefits for an intervention to improve delivery of health promotion services in clinical settings and address a key need. Risks to individual provider participants are minimal.

OBJECTIVES AND ENDPOINTS

We will assess the effectiveness of the THRIVE intervention using the following objectives and endpoints.

Primary Objective: To assess the efficacy of the THRIVE intervention in reducing the cumulative incidence of self-reported non-fatal overdose or skin and soft tissue infection between hospital discharge (baseline) and six months post-discharge, compared to usual care.

Secondary Objective: To assess the effectiveness of the THRIVE intervention compared to EUC at lowering the incidence of the independent outcomes of (1) non-fatal overdoses skin and (2) soft tissue infections.

We will concurrently assess barriers and facilitators to implementation of the THRIVE intervention.

OBJECTIVE	BRIEF DESCRIPTION OF OUTCOME MEASURE	OUTCOME MEASURED BY	TIME FRAME
Primary			
To assess the effectiveness of the THRIVE intervention compared to enhanced usual care (EUC) at lowering the incidence of non-fatal overdoses OR skin and soft tissue infections	Cumulative incidence of non-fatal overdose OR skin and soft tissue infection	Composite measure of: (1) Self-report of at least one non-fatal overdose, OR (2) Self-report of at least one skin or soft tissue infection	From baseline to 6 months
Secondary			
To assess the effectiveness of the THRIVE intervention compared to EUC at lowering the incidence of non-fatal overdoses	Cumulative incidence of non-fatal overdose	Self-report of at least one non-fatal overdose	From baseline to 6 months

OBJECTIVE	BRIEF DESCRIPTION OF OUTCOME MEASURE	OUTCOME MEASURED BY	TIME FRAME
To assess the effectiveness of the THRIVE intervention compared to EUC at lowering the incidence of skin and soft tissue infections	Cumulative incidence of skin and soft tissue infection	Self-report of at least one skin or soft tissue infection	From baseline to 6 months
Exploratory			
Objective	**BRIEF DESCRIPTION OF OUTCOME MEASURE**	**OUTCOME MEASURED BY**	**TIME FRAME**
To assess the effectiveness of the THRIVE intervention on change in **higher risk infection behaviors (characterized by BIRSI score)** compared to EUC.	Higher risk injection behaviors (as characterized by BIRSI)	Total BIRSI score	From baseline to 6 months
To assess the effectiveness of the THRIVE intervention on **HP adoption** compared to EUC.	Health promotion adoption	Number and proportion who: (a) Self-report naloxone use in past 30 days to reverse another person's overdose (b) Self-report of currently carrying naloxone (c) Self-report of using at least one drug checking strategy in the past 30 days	From baseline to 6 months
To assess the effectiveness of the THRIVE intervention on change in **HP access** compared to EUC.	HP access	Number and proportion who: (a) Self-report of having received at least one (naloxone, syringes, new or unused pipes) in past 30 days (b) Self-report of visiting a SSP in past 30 days. (c) Self-report of receiving any HP services from a needle exchange facility in past 30 days.	From baseline to 6 months
To examine heterogeneity of treatment effect by specific sub-population in the THRIVE intervention arm	Cumulative incidence of non-fatal overdose OR skin or soft tissue infection, by specific sub-population	Composite measure of: (1) Self-report of at least one non-fatal overdose, OR (2)	From baseline to 6 months

		Self-report of at least one skin or soft tissue infection	

STUDY DESIGN

6 OVERALL DESIGN

This is a pragmatic, hybrid type I effectiveness/implementation randomized controlled trial (RCT) comparing the Teaching Health promotion and Resilience in Varied Environments (THRIVE) peer-led intervention model to enhanced usual care (EUC). For this phase III RCT, at least N=262 participants from three practice settings will be randomized one-to-one; n=131 to the THRIVE model and n=131 to the EUC arm (see Figure 1), allowing for 25% attrition at 6 months.

Hypotheses:

Primary hypothesis: Individuals receiving the THRIVE intervention will have a reduced risk of self-reported NFOD or SSTI compared to controls receiving EUC at 6 months.

Secondary hypotheses: (1) Individuals receiving the THRIVE intervention will have a reduced risk of self-reported NFOD compared to controls receiving EUC at 6 months, and (2) Individuals receiving the THRIVE intervention will have a reduced risk of self-reported SSTI compared to controls receiving EUC at 6 months.

Study Population: Adult participants (at least N=262) will be recruited from three clinical practice settings: UPMC Presbyterian-Montefiore and UPMC Mercy inpatient and ED settings, and Shadyside inpatient setting. See Section 5 for additional details.

Randomization: Participants will be randomized 1:1 to either the THRIVE intervention or to enhanced usual care (EUC). Randomization will be stratified by clinical setting and method of opioid use (non-injected vs. injected), using a permuted block design with varying block sizes. The randomization allocation will be programmed by the University of Pittsburgh's Center for Biostatistics & Qualitative Methodology's Data Coordinating Center (CBQM DCC) for this study and integrated into the DCC's web-based data collection and management system ("eSYSDM"). Randomization to intervention assignment will occur following baseline assessment and will be displayed to study assessment staff. Intervention arms are not masked.

7 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A Hybrid Type 1 effectiveness-implementation trial was chosen as it allows for us to assess whether the THRIVE intervention works pragmatically, and it also allows us to collect information on how to effectively implement THRIVE in clinical settings moving forward. In the context of clinical trials, this type of trial design is particularly valuable in bridging the gap between research and practice, which is essential in light of rising overdose deaths requiring urgent interventions to implement innovative practices and improve delivery of care.

The trial aims to evaluate the clinical efficacy of the THRIVE intervention under pragmatic, real-world conditions. The THRIVE intervention contains components that individually have been found to be effective (e.g., naloxone distribution to reduce overdose risk), but are now being tested in combination. These will be delivered by a PWLE who will serve in a peer support specialist role. There is a robust body of literature describing the integration of PWLE in health promotion services[20,21] in ways that increase feasibility, acceptability and quality of services provided to PWUD.[22] We will be primarily testing the effectiveness in a Hybrid Type 1 trial while concurrently measuring challenges and facilitators to implementation. The study aligns with Curran et al.'s recommended criteria for Hybrid Type 1 Clinical Trials: 1) the intervention has strong face validity; 2-3) there is a strong rationale for application of these intervention components in this clinical setting and for this patient population, and 4) there is minimal risk.[42]

8 JUSTIFICATION FOR INTERVENTION

The THRIVE Intervention: The THRIVE intervention was co-created with PWLE (defined as current or historical drug use). They helped design the delivery method, length, number, and frequency of intervention contents. Data suggests that incorporating the perspectives of PWLE in the co-creation process will lead to greater likelihood of success, including more recruitment of participants across various populations, improved study retention,[35–37] and greater likelihood of research leading to changes in policy and practice.[38–40] We will deliver the first contact with participants face-to-face as it is was deemed important to building rapport and establishing a strong relationship between study participants and the THRIVE peer support specialist. The peer support specialist will then follow up with weekly text messages over 12 weeks as this time was deemed both reasonable to observe possible changes in behavior but not too long to lose participants. The intervention is semi-structured and participant-led, so length of time of each contact may vary based on how engaged participants are in the process. Participants that receive the initial face-to-face session will be considered as they received the "minimum" amount necessary to be included in the intervention.

Enhanced Usual Care (EUC): Usual care for participants seen in the hospital setting or ED is often piece-meal delivery of health promotion referrals and resources. In the EUC arm, all participants will receive basic information on how and where to access health promotion resources and supports via a pamphlet. Information will include how to access health promotion services locally and via mail, as well as information on how to use fentanyl test strips and naloxone.

9 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if they have completed the baseline and 6-month assessments. The end of the study is defined as completion of the 6-month follow-up assessment, shown in the Schedule of Activities (SoA), Section 2, by the last randomized participant, approximately 36 months from the opening of study enrollment.

STUDY POPULATION

We will recruit at least 262 patients from UPMC Presbyterian-Montefiore and UPMC Mercy inpatient and ED settings, and UPMC Shadyside inpatient setting. We will only be recruiting adults over the age of 18 as our focus is on hospitals serving adults. No other groups will be excluded.

At the study conclusion, we will survey approximately 100 clinicians, staff, and/or administrators from each of five participating settings (EDs and inpatient stays) regarding challenges and facilitators to implementation of the THRIVE model.

10 INCLUSION CRITERIA

10.1.1 Patients

To be eligible to participate in this study, a patient must meet all of the following criteria:

1. Patients who are: a) admitted to UPMC Shadyside Hospital, UPMC Presbyterian-Montefiore Hospital, UPMC Mercy Hospital for inpatient or observation status, or b) seen in the ED setting at UPMC Presbyterian-Montefiore Hospital and UPMC Mercy Hospital.
2. Patients must have a current diagnosis of OUD based on DSM-5 diagnostic criteria.
3. Patients must be at least 18 years of age on day of admission.
4. Patients must be able to speak and read English.

10.1.2 Providers

In order to be eligible to participate in this study, a provider must meet all of the following criteria:

1. Providers must be employed by UPMC Shadyside Hospital, UPMC Presbyterian-Montefiore Hospital, and/or UPMC Mercy Hospital.
2. Provide direct patient care (e.g., social worker, physician, nurse, nurse practitioner, physician assistant, medical assistant) in the hospital or ED setting.

11 EXCLUSION CRITERIA

11.1.1 Patients

A patient who meets any of the following criteria will be excluded from participation in this study:

1. Patients diagnosed with dementia and/or cognitive impairments.
2. Patients with acute psychiatric complications, such as schizophrenia with acute psychosis, acute mania, or suicidal ideation (which may impact the ability of a participant to consent and actively participate in treatment).
3. Patients who are pregnant or lactating at onset of study.
4. Patients who cannot read or speak English.

11.1.2 Providers

A provider who meets any of the following criteria will be excluded from participation in this study:

1. All providers who meet the above inclusion criteria will be eligible to participate.

12 INVOLVEMENT OF VULNERABLE PARTICIPANTS

Vulnerable populations, as defined by the IRB, may include individuals who, due to their circumstances, are at an increased risk of coercion, undue influence, or potential harm. This population may include individuals with cognitive impairments, minors and adolescents, those who are pregnant or lactating, and those with limited decision-making capacity; however, none of these groups will be included. We will be recruiting individuals that have specific economical and social needs. We will carefully choose a

compensation method that fairly compensates for individual time, but will not be coercive. We will choose these compensation amounts with guidance from an advisory board of PWLE. We will give individuals sufficient time to read through the consent form, to ask questions, and to feel comfortable with the consent process.

13 Involvement of Pregnant Participants, Babies in Utero, or Neonates

We will not include pregnant participants during enrollment of the study period. If participants become pregnant during the study period, we will offer to connect them to pregnancy-focused resources. Individuals will not be excluded from the study, however, if they remain in the study, we will continue to offer pregnancy-related resources at each study visit.

14 Lifestyle Considerations

Not applicable.

15 Screen Failures

Screen failures are defined as participants who:

- Do not meet the eligibility criteria for participation in the study, or
- Consent to participate in this study but are not subsequently assigned to the study intervention (e.g., discharged before assignment to intervention arm, or leave against medical advice [AMA]), or
- Screen eligible but then decline to enroll in the study

16 Strategies for Recruitment and Retention

Patient Recruitment: Study team members will review patients currently being seen in the emergency department or those being seen by pertinent consult teams (e.g., Addiction Medicine Consult Service at UPMC Montefiore-Presbyterian, Psychiatry Liaison Service at UPMC Shadyside, Inpatient detox and Toxicology at UPMC Mercy) to identify those who may be potentially eligible. They will then approach patients to explain the study and ask their interest in learning more and completing screening.

Patients will be recruited during the acute hospitalization or emergency department stay. Project flyers/ posters with contact information will be posted in participating ED waiting areas and exam rooms. The flyers/posters will have contact information, including a website and QR code where interested patients could learn more about the study and express their desire to be contacted. Providers and inpatient/ED staff will be educated about the project and eligibility criteria to encourage direct referral of patients for screening, particularly those presenting with any complaint related to opioid use. We will also provide flyers/posters for inpatient teams to give potentially eligible patients.

If individuals are interested in participating, we will ask hospital staff to send us a text or call our study work phones and will then have someone from the study team meet the patient in-person at bedside. We will conduct screening and provide additional information on the study. For patients interested in participating, we will have an informed consent conversation. For patients who consent, we will obtain follow-up telephone numbers for the patient and three other contacts and obtain permission to contact the contacts if we are unable to reach the patient after three attempts to their personal number or address. Our goal is to enroll at least 262 patients.

Provider Recruitment: At study conclusion, we will reach out via electronic correspondence, noon conferences, and hospital listservs to recruit healthcare providers who wish to participate in a survey. We will use the listserv for given units (including ED) to send out a link for an anonymous electronic survey. Healthcare providers will be asked to complete informed consent electronically and complete an electronic survey on implementation barriers to delivering the THRIVE intervention in their clinical setting.

16.1.1 Costs

Participants will not incur any costs associated with their participation in this study.

16.1.2 Compensation

Patient participants will be reimbursed a total of $260 for participation in the trial via gift card. They will be reimbursed $55 for the initial baseline assessment, $65 for the 3-month follow-up, and $85 for the 6-month follow-up assessment. They will receive $20 for completing each automated monthly text message survey and an additional bonus of $5 per survey if the prior month's survey was also completed. Compensation was determined based on input from key advisors to avoid coercion but to fairly reimburse participants for their time.

Healthcare provider participants will be compensated with a $10 gift card at the conclusion of the study period for participating in an electronic survey. The provider survey responses will be kept separate from their contact information for gift card delivery.

STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

17 STUDY INTERVENTIONS(S) OR EXPERIMENTAL MANIPULATIONS(S) ADMINISTRATION

17.1.1 Study Intervention or Experimental Manipulation Description

The THRIVE Intervention: The THRIVE intervention was co-created with PWLE (defined as current or having a history of drug use). They helped design the delivery method, length, number, and frequency of intervention contents. Data suggests that incorporating the perspectives of PWLE in the co-creation process will lead to greater likelihood of success, including more recruitment of different participants, improved study retention,[35–37] and greater likelihood of research leading to changes in policy and practice.[38–40] We will deliver the first contact with participants face-to-face, as it is was deemed important to building rapport and establishing a strong relationship between study participants and the THRIVE peer support specialist. The peer support specialist will then follow up with weekly text messages over 12 weeks, as this time was deemed both reasonable to observe possible changes in behavior but not too long to lose participants. The intervention is semi-structured and participant-led, so length of time of each contact may vary based on how engaged participants are in the process. The intervention is derived from the Capacity-Opportunity-Motivation- Behavior (COM-B) model and Theoretical Domains Framework (TDF),[39–41] which suggests that offering education that focuses on improving knowledge and skills (capability); altering social influences and environmental contexts to access health promotion services (opportunity); and changing beliefs about consequences of drug use, self-efficacy in using health promotion strategies, feelings about social uniqueness, and emotions (motivation), will lead to change behaviors that promote health and reduce harms around substance use. Specific change behaviors include increasing adoption of naloxone and overdose prevention strategies, and the reduction of skin and soft tissue infections via greater adoption of safer injection practices.

The enhanced control condition involves delivery of basic information on how and where to access health promotion resources and supports via a pamphlet. Information will include how to access health promotion services locally and via mail-service, as well as information on how to use fentanyl test strips and naloxone.

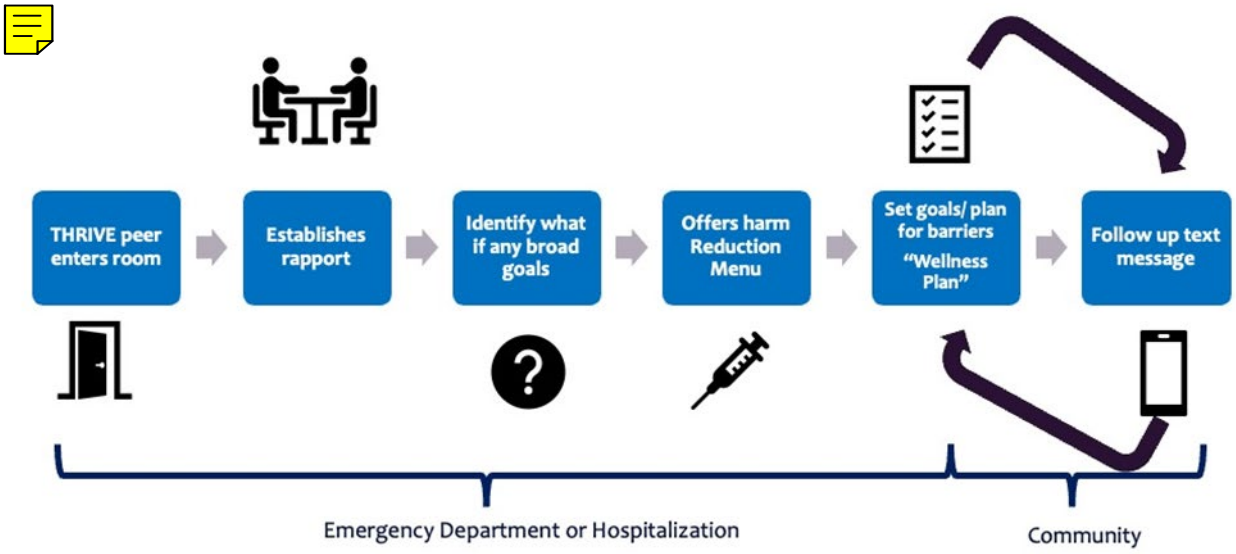
17.1.2 Administration

The THRIVE intervention will be semi-structured. The initial face-to-face session will allow for study participants to guide the specific health promotion information received from a set menu of health promotion topics, so the specific length of time for the initial face-to-face session will vary by participant

selection. The weekly peer text messages will be structured initially but allow for flexibility with how the peer support specialist responds to participants—responses will include support for goal setting or troubleshooting challenges, linking study participants to needed resources in their local area, and providing lay psychosocial support/motivational interviewing for related experiences.

A complete intervention dose is defined as receiving the face-to-face session followed by engagement, defined as reading and responding to, weekly peer text messages for a total of 12 weeks. We will track responses to weekly text messages as a way to measure dose and intensity.

Participants will not be interacting with other trial participants and will have primary contact through one THRIVE peer support specialist.



18 FIDELITY

18.1.1 Interventionist Training and Tracking

Monitor for protocol fidelity. Dr. Wilson will monitor fidelity using best practices from the NIH Behavior Change Consortium. She will create a tracking sheet with associated checklists to monitor adherence to THRIVE protocols for delivery, monitor delivery of the THRIVE content, and monitor adherence to sequencing and follow-up. Peer specialists will capture audio recordings of some intervention sessions to be reviewed for this purpose. They will confirm participants' willingness to be recorded prior to starting the session. Fidelity assessments will be conducted by the principal investigator and trained staff members. Research staff will review intervention audio recordings, shadow some intervention sessions, and use the fidelity checklist to monitor adherence, content, and skill use. The checklist will record if components are present and then will rate the quality of delivery using a five-point Likert scale. If staff-specific fidelity rates fall below 85%, Dr. Wilson will retrain staff to ensure they meet appropriate fidelity to THRIVE protocol and/or study assessments.

Monitoring missingness (patterns and quantity). An assessment will be made of the scheduled data collection identifying discrepancies between planned and actual assessment dates, and on the percent of

successful versus unsuccessful completion of assessment instruments. We will use this to identify problems with retention that require a study wide intervention vs staff retraining. We will also identify missing data values due to lack of responses to particular items. We will identify possible non-random patterns of missing data. When items or staff members are associated with more than 8% missing data than unexpected for skip patterns, we will determine the causes and implement strategies to reduce it, including possible retraining of staff and discussions with the THRIVE Community Advisory Board (CAB) to discuss language around these items. Completed assessments will be reviewed periodically by the PI and/or Co-Is, and any administration errors that are detected will be addressed.

Monitoring reliability and construct validity of Key Measures. We plan to perform reliability checks on research instruments. We will review completion rates for questions. If an aberrant response pattern is identified, we will check data entry procedures. Second, we will examine descriptive statistics to examine if there is a restriction in the range of responses for the current sample. This will then allow us to investigate if this is a problem with understanding the specific instrument language or a reflection of system-wide assumptions. We will discuss the problem with the CAB to discuss potential interventions based on our findings.

Measures to Minimize Bias: Randomization and Blinding

Randomization

1. Approved study staff will randomize the participant to the THRIVE or EUC arm using the electronic data capture system, eSYSDM.
2. A stratified, randomized block design will be used to assign participants to one of the two intervention arms and will be stratified by clinical practice setting (defined as hospital site) and method of opioid use (non-injected vs. injected) using randomly permuted block sizes.
3. Research staff will access their site-specific randomization module in the eSYSDM. Staff will enter which the participant's preferred method of opioid use (injected or non-injected) and the intervention arm assignment will be generated.
4. Enrollment will be continuous with the goal of reaching the desired sample size.

Blinding

The baseline interview will occur prior to randomization to ensure research staff are blind to the study condition. Follow-up interviews will be performed by research staff who initially will be blinded to study condition, although such blinding may be broken during the course of the follow-up interview if patients disclose participation in THRIVE.

Minimization of Assumptions

It is likely (and expected) that medical teams will treat patients in both the THRIVE and EUC conditions. Patients in the THRIVE condition will have an enhanced experience because they, unlike patients in the EUC condition, will receive the baseline THRIVE intervention components designed to support their problem-solving and goal-setting around health-promoting behaviors. As this intervention will be delivered directly to the patient participants, there will not be messaging about their participation available to the medical teams. The content of the messaging is focused on health promotion broadly and contains content around MOUD. By definition, the content offered will be patient-directed. Even as medical teams become more aware of MOUD and health promotion practices throughout the course of the intervention, we hypothesize that patients who are randomized to the THRIVE intervention will not be more likely to receive medications or other interventions from their healthcare teams at rates greater than the EUC group. Thus, over time, we might see increased medication initiation or increased provision of naloxone for patients in both study groups. The specific tailored content of THRIVE is focused on offering health promotion education and following up on individual goals after discharge, so the intervention should not influence

patient behavior during the hospital stay. We theorize it may lead to increased follow-up or engagement in services after hospital discharge.

Study Intervention/Experimental Manipulation Adherence

Participants will be considered in the study once they complete their baseline assessment and are followed for 6 months. While we will do an intent-to-treat analysis, we will also perform a modified intent-to-treat analysis that includes only those participants who were able to complete the initial face-to-face intervention. We will calculate intervention exposure by calculating the number of patient contacts completed divided by the total possible number of patient contacts (one face-to-face intervention and 12 text-based contacts).

19 CONCOMITANT THERAPY

Not applicable.

20 RESCUE THERAPY

Not applicable.

STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

21 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

When a subject discontinues from the THRIVE intervention, but not from the study, remaining study follow-up assessments will still be administered. If a clinically significant finding, such as changes from baseline, is identified after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding meeting the definition of an Adverse Event (AE) will be reported.

The data to be collected at the time of study intervention discontinuation will include the following:

- The reason(s) for discontinuing the participant from the intervention
- If the participant is due to complete assessments within two weeks of being discontinued from the study intervention, those assessments will be administered at the time of discontinuation. If the next scheduled assessments are more than two weeks from the discontinuation date, the discontinued participant will wait for the next scheduled assessment. Thereafter, the participant will be included in all future scheduled assessments, even though not participating in the intervention.

22 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue a participant from the study for the following reasons:

- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- Participant incarceration, which extends beyond the follow-up period
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- The participant is deceased

The reason for participant discontinuation or withdrawal from the study will be recorded on the Study Status Case Report Form (CRF). Subjects who provide consent and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and

receive the study intervention, and subsequently withdraw, or are discontinued from the study, will not be replaced.

23 LOST TO FOLLOW-UP

In general, a participant will be considered lost to follow-up at the end of their study period at the time of their last completed study assessment. This will be determined programmatically at the time of the primary analysis. There may be cases where contact attempts are unsuccessful following missed assessments and the study staff may mark the participant as "lost to follow-up" in the Study Status CRF at the conclusion of their intervention period (will be done retrospectively if no responses to contact able to be made).

The following actions must be taken if a participant fails to respond to scheduling request for a required study visit:

- The study team will attempt to contact the participant and reschedule the missed visit in the time frame allotted for each assessment (See Table 1), counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain if the participant wishes to and/or should continue in the study.
- The investigator or designee will make every effort to regain contact with the participant with at least three telephone calls at each missed contact, at least one call to each of the back-up contacts, if necessary, three contacts via social media (e.g., e-mail, Facebook, Instagram), and a letter to the participant's last known mailing address (or local equivalent methods). These contact attempts should be documented in the participant's study record.
- Should the participant continue to be unreachable, at the end of the study he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

STUDY ASSESSMENTS AND PROCEDURES

24 SCREENING PROCEDURES

24.1.1 Screening activities performed prior to obtaining informed consent

Clinical providers will refer potentially eligible patients to the study team (these include both ED and hospitalist providers).

24.1.2 Screening activities performed after a verbal consent for screening has been obtained

Patient Participants: Once consent has been obtained, the participants will complete screening to confirm eligibility. Screening questions will be completed electronically by the study assessment staff. For patients who are not screened as eligible, they will be thanked for their time and given a paper handout detailing health promotion resources. For those who are screened as eligible, they will then complete informed consent.

Provider Participants: The first two questions on the clinician survey form will confirm their eligibility. For those who do not meet criteria, the survey will end.

25 STUDY EVALUATIONS & PROCEDURES

Following initial screening for inclusion/exclusion criteria, study assessment staff will obtain informed consent (including permission to send text messages to participants) and enroll at least 262 patients during the study period (with enrollment criteria as described above). Once potential participants are identified, screened for eligibility, and provide informed consent, they will complete a baseline assessment to complete enrollment. We will collect multiple phone numbers and contacts for each participant in order to maintain

contact through the intervention and follow-up periods. Once the baseline assessment is complete, they will be randomized 1:1 to either the THRIVE arm or EUC.

Participants randomized to the THRIVE intervention will receive the first in-person face-to-face session after completing the baseline assessment. This session is semi-structured and led by a PWLE, defined as a THRIVE peer support specialist. The THRIVE peer support specialist will begin by building rapport with study participants where they may ask questions about their lives, share their own previous history of substance use disorder and recovery, and find commonalities. They will solicit what, if any, goals participants may have around their wellness and then will offer information and resources on several health promotion topics selected by the patient from a menu of topics. Participants will then complete a Wellness Plan focused on a specific wellness goal and will plan for addressing potential challenges. Participants will receive weekly text messages from the peer support specialist for the next 12 weeks focusing on goal setting from the week prior, progress meeting goals, and associated behavioral challenges. While the opening weekly peer text messages will be structured, THRIVE peer support specialists will then respond to participants conversationally.

All participants, regardless of study condition, will be sent questions each month via an automated text message platform. Questions will ask about any history of non-fatal overdose, injection drug use, or any present skin and soft tissue infection, regardless of injection site, in the past 30 days. Participants will be scheduled for assessments at 3 months and at 6 months. These can be completed in-person or by telephone.

At conclusion of patient enrollment, we will distribute an anonymous electronic survey to healthcare providers serving each of the clinical settings used for recruitment. Healthcare providers will be asked to complete informed consent electronically prior to completing the survey. The survey will include questions from the Organizational Readiness for Change Assessment and the Acceptability of Intervention Measure and Intervention Appropriateness Measure to identify what implementation challenges existed during the trial and to identify possible implementation supports to improve implementation in future trials.

25.1.1 Biospecimen Evaluations

Not applicable.

25.1.2 Samples for Genetic/Genomic Analysis

Not applicable.

26 SAFETY ASSESSMENTS

We are not doing safety assessments and will not be asking questions about suicidality as a routine part of the study. We will collect AEs (see section 1.25.1). Additionally, if a patient spontaneously discloses suicidality, we will deploy the following management plan:

If participants disclose to study assessment or study intervention staff either (a) suicidal ideation or suicidal thoughts, or (b) action, including both thoughts of suicide, and the presence of a plan and/or means to complete suicide, study staff will immediately disclose information to the PI and Project Coordinator who holds a license in social work practice (LSW). Based on the information disclosed and location of the participant, there will be an immediate follow-up inquiry with the participant to further determine level of risk. If the participant is located in the hospital setting, this information will be immediately relayed to the hospital staff providing care to the patient so appropriate assessment and protection measures are enacted. As the participant is actively receiving care in that setting, study staff will stay with the participant until appropriate notification can be made, and the participant's medical team can come to the bedside to assume responsibility and care. If the participant is remote and there is sufficient evidence to suggest an immediate risk of suicidal action, study investigators (the PI or locally-based Co-Investigators on the study team) will develop a safety plan with the participant and make indicated referrals, which may include referral to the Pittsburgh crisis hotline for a mobile evaluation, or

calling emergency medical services via 911 for immediate assessment and transfer to the hospital for evaluation. If the disclosure is the result of one of the written assessment items in the study, the study assessment staff will relay concerns to PI and the Project Coordinator who will contact the participant by phone to clarify intention or action. If, upon further review with the study participant, the participant endorses passing suicidal thoughts, but denies any presence of plan or means to complete suicide, and actively endorses a plan to connect to safety supports, the PI and Project Coordinator may create an alternative safety plan focused on linking participants to crisis supports within the community.

Intervention Staff: During intervention sessions, interventionists will be required to engage the PI and Project Coordinator if there becomes concern about suicidal ideation or actions and will then follow the same steps listed above.

ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

26.1.1 Definition of Adverse Events (AEs)

Federal regulation (21 CFR Part 312) defines an "Adverse Event" (AE) as any untoward occurrence involving a study participant, or individual connected to the participant, occurring during the course of the study and study follow-up period. AEs may be unanticipated. AEs are categorized as either a Serious Adverse Event (SAE) or an Adverse Event (AE). SAEs are negative experiences that involve imminent danger. AEs are defined as negative experiences that do not involve imminent danger.

AEs may be potentially identified during interviews with study staff, contact for tracking or scheduling study assessments, or during regular contacts with THRIVE peer support specialists. AEs may or may not have a causal relationship with any THRIVE study activities. Any events may be brought by any study staff or the research investigator team.

Possible AEs involving human participants include:

- Serious physical injuries; worsened physical health or mood/affect; suicidal ideation or attempts; markedly increased substance use; worsening anxiety with panic attacks; increased signs of depression; adverse drug reactions; markedly increased sexual risk behavior; and/or marked abnormalities in biological tests.
- Other, non-clinical AEs may include the inadvertent disclosure by research staff of confidential research information to other persons, or harassment from members of the local area based on a participant's diagnosis of OUD. Breach of confidentiality is a risk, although highly unlikely, due the safeguards described in the Protection of Human Subjects section.

26.1.2 Definition of Serious Adverse Events (SAE)

An SAE is defined as an event that may involve imminent danger to self or others.

Child abuse and child neglect is defined as current physical or sexual abuse or neglectful behaviors on the part of an adult to a child. These may include, but are not limited to, injuries inflicted by hitting, kicking, burning, shaking or throwing, use of a weapon against a child, inappropriate sexual contact, and failure to provide food, shelter or medical care that is necessary for the child's survival.

A life-threatening event may include: intentional or unintentional injury, suicidal threat or behavior with confirmed intention or plan, or fatal drug overdose; serious violent behaviors directed toward another including any threats, ideations, or attempts to seriously injure or kill another person; hospitalizations or medical events that require or prolong inpatient hospitalization, persistent or significant impacts to activities of daily living or incapacity (including terminal illness); and death.

Non-clinical SAEs will also be closely monitored, tracked, and addressed. Examples of potential non-clinical SAEs include stigma or threats from others that could lead to violence toward a participant due to the participant being identified as a person with an OUD. If the outcome of the

event meets the typical definition of an SAE, it would be treated as an SAE. Otherwise, this would be treated as a reportable event.

As described above, the PI (Wilson), in collaboration with the Co-Investigators, will oversee all procedures designed to continuously monitor participant safety. All AEs, SAEs, and reportable events will be tracked in the study database. The research team will have regular meetings to discuss actual or potential issues that may affect participants' safety. During these meetings, Dr. Wilson will review the progress of all study participants, including relevant data obtained for each participant, to ensure adherence to all standards for maintaining participants' safety and confidentiality.

26.1.3 Classification of an Adverse Event

26.1.3.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require intensive drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious."

26.1.3.2 Relationship to Study Intervention/Experimental Manipulation

All AEs will have their relationship to study procedures, including the intervention, assessed by an appropriately trained clinician based on temporal relationship and their clinical judgment. The degree of certainty about causality will be graded using the categories below.

Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.

Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.

Potentially Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.

Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

Not Related – The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

26.1.3.3 Expectedness

A clinician with appropriate expertise in addiction medicine will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

26.1.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while in the study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

Study staff will record events with start dates occurring any time after randomization until their final day in the study. At each study visit, the study staff will identify any AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

26.1.5 Adverse Event Reporting

In the event of an AE, research staff will obtain as much information as possible about the nature and timing of the event, potential contributing factors, and the current status of the participant. AEs will be followed until the condition ends or stabilizes with no more expected improvement. These time periods, in our experience, are adequate to determine if any consequences of the AE are adequately followed through. AEs will be summarized and listed in monthly study reports. They will also be summarized and listed in DSMB reports.

26.1.6 Serious Adverse Event Reporting

In the event of an SAE, research staff will obtain as much information as possible about the nature and timing of the event, potential contributing factors, and the current status of the participant. In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of an SAE and shall report the results of such evaluation to the Sponsor and the NIH Institutional Review Board (IRB) as per Policy 801. SAEs will be followed until the condition ends or stabilizes with no more expected improvement. These time periods, in our experience, are adequate to determine if any consequences of the SAE are adequately followed through. In the event that an SAE is reported to the study research team, they will communicate the event to the IRB within 24 hours and enter the information into the appropriate CRF. If the event is determined to be an SAE that is study-related, the PI (Wilson) will report the event by email

to the NIDA Project Officer within 48 hours. All SAEs and AEs that are determined to not be related to study activities will be reported to NIDA in the annual Progress Reports.

26.1.7 Events of Special Interest

Not applicable.

26.1.8 Reporting of Pregnancy

While participants will not be included if pregnant at baseline, if patients become pregnant during the course of the study, we will complete the pregnancy reporting form. We will offer participants additional resources and referrals to the Pregnancy Recovery Center if desired, which provides comprehensive supports to pregnant individuals with OUD.

27 UNANTICIPATED PROBLEMS

27.1.1 Definition of Unanticipated Problems (UP)

Any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; and
- Related or possibly related to participation in the research. "Possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research; and
- Suggests that the research places participants or others (which many include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social) than was previously known or expected.

27.1.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the NIH Institutional Review Board (IRB) as per Policy 801.

STATISTICAL CONSIDERATIONS

28 STATISTICAL HYPOTHESIS

28.1.1 Primary Hypothesis

Individuals receiving the THRIVE intervention will have a reduced risk of self-reported NFOD or SSTI (composite outcome) compared to controls receiving EUC at 6 months. We will test the following statistical hypothesis,

$$H_0: HR_{\text{Composite}} = 1$$

$$H_1: HR_{\text{Composite}} \neq 1$$

Where HR is the hazard ratio comparing the risk of the composite outcome in the THRIVE intervention arm to the control arm. We expect the HR<1 but have powered for a two-sided test.

28.1.2 Secondary Hypotheses

1. Individuals receiving the THRIVE intervention will have a reduced risk of self-reported NFOD compared to controls receiving EUC at 6 months.

2. Individuals receiving the THRIVE intervention will have a reduced risk of self-reported SSTI compared to controls receiving EUC at 6 months.

28.1.3 Exploratory Hypotheses

1. Individuals receiving the THRIVE intervention will have lower high risk injection behaviors (BIRSI score) compared to controls receiving EUC at 6 months.

2. Individuals receiving the THRIVE intervention will have greater HR adoption compared to controls receiving EUC at 6 months.

3. Individuals receiving the THRIVE intervention will report greater HR access compared to controls receiving EUC at 6 months.

4. Because of cultural adaptation, there will be minimal heterogeneity of treatment effect by specific sub-groups.

29 SAMPLE SIZE DETERMINATION

29.1.1 Original Sample Size Justification

Literature suggests that at a given time, approximately 32% of persons with IDU have a current SSTI[43] and between 20%-37% experienced at least one SSTI in the past 6 months.[43,44] Independently, a recent epidemiological study found that the incidence of any NFODs in past 12 months was 36.9%.[45] We will assume that at 6 months, the rate is half that (18.5%). The incidence of both events occurring during a given time span (6 months or 12 months) is unknown. Should the probabilities of SSTI and NFOD be independent, their joint probability of occurring may be between 0.037 and 0.068 based on the incidences reported above. Thus, it follows that the probability of SSTI or NFOD occurring (the composite outcome) may be between 0.385 and 0.555 in this situation. It is unknown what the level of dependence is between these events in a given person (i.e., the probability that both events occur in a given person during this time period). If we assume the joint probability of SSTI and NFOD is between reasonable estimates of 0.037 (independent) and 0.20 (dependent), this is analogous to probabilities of any SSTI or NFOD between 0.185 and 0.485 in a control arm. To err on the conservative side, we assume the composite event rate in the control arm is on the lower end (0.285) and hypothesize we will see an relative rate reduction in the intervention arm of 45%, corresponding to a hazard ratio (HR) of 0.509. Using a two-sided test of whether the HR=1, we will randomize 262 participants (131 per arm) which includes an inflation adjustment for 25% attrition. Additional assumptions include that the HR is constant throughout the study, power=0.80, and a type I error rate=0.05. We require 156 per arm for the primary analysis.

For the key secondary measures of cumulative incidence of SSTI alone and, separately, NFOD alone at 6 months, with an analysis sample size of 156 per arm, power=0.80 and a type I error=0.05 we can detect an relative rate reduction of 45% in each of NFODs and SSTIs in the intervention vs. control arms. This assumes the cumulative incidence of NFODs is 0.185 in the control arm and 0.102 in the intervention arm (HR=0.433); and for SSTIs, assumes 0.285 in the control arm and 0.157 in the intervention arm (HR=0.509)

29.1.2 Updated Sample Size Justification

Based on extenuating funding circumstances, the study team determined that the full study period must end earlier than originally planned. Therefore, we determined the need to reassess our original assumptions regarding sample size requirements to assure that we would be adequately powered to test our hypotheses given potentially fewer participants in the study. As of March 2026, looking at only our control arm participants, we had 23.3% with NFOD (secondary outcome 1), 44.2% with SSTI (secondary outcome 2), and 51.2% with NFOD or SSTI (primary outcome) by the 6-month primary time point. Our original assumption was that 28.5% would experience NFOD or SSTI by this point. Additionally, our attrition rate by 6 months was approximately 35%.

The table below presents several different scenarios based on varying effect sizes. Our updated target sample size of N=262 (red box and text below) retains the 45% relative reduction in NFOD or SSTIs while accounting for the increased attrition and observed control arm incidence of the primary outcome.

	Hypothesized Enhanced Usual Care proportion of participants with any NFODs or SSTIs at 6 months	Hypothesized THRIVE intervention arm proportion of participants with any NFODs or SSTIs at 6 months	Hypothesized Hazard ratio (HR) corresponding to proportions (% risk reduction at 6 months)	Total enrolled and randomized sample size to allow for 25%* attrition	Total needed to enroll with 35% attrition	Relative % reduction	Endpoint total sample size required for analysis (per arm)	Endpoint total sample size required for analysis
Original Solved for sample size based on hypothesized HR	0.285	0.157	0.509 (50.9%)	390	422	45%	156	312
New estimate based on control group NFOD or SSTI rates at 6 months	0.512	0.157	0.362	116	126	69%	46	92
	0.512	0.281	0.527	244	262	45%	97	194
	0.512	0.307	0.567	300	324	40%	120	240
	0.512	0.333	0.609	380	412	35%	152	304

* In original sample size estimates, our calculations included a 25% attrition but we mistakenly wrote a 20% attrition. All estimates in this column are with 25% attrition

30 POPULATIONS FOR ANALYSES

The primary analysis population will be intention-to-treat (ITT). This includes all participants randomized to either THRIVE or EUC. We will also perform the analysis in a modified ITT, which includes all participants who are randomized and received the initial (face-to-face) intervention.

31 STATISTICAL ANALYSES

31.1.1 General Approach

Descriptive statistics will be used to summarize data: means, standard deviations, medians, and quartiles for continuous data; frequencies and percentages for categorical data. Baseline characteristics will be reported overall and by arm where they will be assessed for imbalance via appropriate methods (t tests, ANOVA, Wilcoxon Rank Sum tests or Mann Whitney tests for continuous data; chi-square or Fisher's exact tests for categorical data). Attrition will be compared between the arms, identifying any baseline covariates that may be associated with loss-to-follow-up. Variables associated with attrition will be included as fixed covariates in the primary and secondary analysis models to mitigate bias due to drop-out. The type I error level will be $\alpha = 0.05$ and 95% confidence intervals will be reported. Analyses will be performed in R 4.0 or higher and/or SAS 9.4 or higher.

31.1.2 Analysis of the Primary Endpoints

The primary endpoint is the cumulative incidence (incidence proportion) of the composite measure of: (1) at least one self-reported episode of NFOD in between baseline and 6 months, OR (2) at least one self-reported episode of skin or soft tissue infection (SSTI) between baseline and 6 months. This composite measure will be assessed monthly via text message assessments captured by two questions: 1) "In the last month, have you overdosed by accident (i.e., where you had a negative reaction from using too much drugs)?"[45] and 2) "In the last month, did you have an abscess related to injection drug use (including any hard, infected lumps that contain pockets of pus or enduring lumps, even if they did not "come to a head," drain, or require treatment of any kind), ulcers (open infected sores), cellulitis (more widespread skin infection) or other infections related to injection?"[6,7,44]

The intention-to-treat (ITT) principle will define the primary analysis population. The primary endpoint is cumulative incidence from baseline to 6 months of any SSTI OR NFOD. A Cox proportional hazards model will be fitted to the composite outcome, with monthly observations between baseline and 6 months. Stratification variables by site and whether participant reports IDU in the last month at baseline will be included as fixed covariates in all models. Additional fixed baseline covariates to be included in the model are age, sex, race/ethnicity composite, housing status, level of education, comorbid substance use, depression, anxiety, and post-traumatic stress disorder. Interactions between treatment arm and race/ethnicity will be included to assess heterogeneity of treatment effect. The cumulative incidence and 95% confidence interval of the composite event will be reported for each arm. The HR and 95% CI comparing the arms will be reported, as well as the relative risk reduction for interpretability. We will assess the proportional hazards assumption. If the assumption is mildly violated, a single HR will likely still be informative;[46] however, we may also include a time × treatment arm interaction[47] to understand how the risks change over time. Should these methods be insufficient, alternative models will be applied, such as an accelerated failure time model.

31.1.3 Analysis of the Secondary Endpoint(s)

The cumulative incidence of NFOD alone and SSTI alone between baseline and 6 months are key secondary endpoints. The components of the primary composite outcome (SSTI, NFOD) will be assessed individually per the methods described for the primary analysis and similar statistics will be reported.

31.1.4 Safety Analyses

Not applicable.

31.1.5 Baseline Descriptive Statistics

Baseline summary statistics are described in section 31.1.1. Variables of interest include:

Sex	Education	PTSD
Race/ethnicity composite	Housing status	History of sex work
Age	Co-morbid substance (non-opioid) use	Sexual orientation
Gender identity	Depression	Housing insecurity
IDU last 30 days	Anxiety	Food insecurity
		Employment status

31.1.6 Planned Interim Analyses

There are no planned interim analyses for effectiveness or futility.

Sub-Group Analyses

Heterogeneity of treatment effect by specific sub-groups in the THRIVE intervention arm will be assessed. The primary analysis earlier described will be applicable here: specific sub-group and its interaction with treatment arm will be included as covariates in the Cox proportional hazards model. The HR for the interaction term and 95% CI will be reported. If the interaction is not significant at the α=0.05 level of significance, that is evidence there is no heterogeneity of treatment effect by sub-group. Similarly, we will perform these same analyses and report the same statistics for the two key secondary outcomes.

31.1.7 Exploratory Analyses

For the patient-reported outcomes measures, the endpoints are the changes from baseline to 6 months of these measures. Linear mixed models will be fitted to the outcome measures, incorporating observations from baseline, 3 months, and 6 months. Normality assumptions for the outcome variables will be assessed and normal transformations will be performed as appropriate. Continuous outcomes will be assessed with linear mixed models. Categorical outcomes will be assessed with mixed (multinomial as appropriate) logistic regression models. All models will include the stratification variables site (defined as hospital) and whether participant is a PWID. Additional covariates to be included in the model are age, sex, race/ethnicity, level of education, housing status, comorbid substance use, depression, anxiety, and post-traumatic stress disorder. Interactions between treatment arm, length of time, and race/ethnicity will be included to assess differential treatment effects over time and heterogeneity of treatment effects. Contrasts between baseline and 6 months, along with their 95% confidence intervals, will be reported to estimate the treatment effect for each outcome measure. We may assess whether time-varying covariate data should be included in modeling incidence rates and, if so, appropriate methods will be used (e.g., frailty or AFT models).

31.1.8 Missing Data

For participants who are lost to follow-up or miss responding to the monthly text message assessment, we will query EHR data to identify any NFOD and/or SSTI for which participants sought medical attention. We will use these as a surrogate for the self-reported data. Intermittent missing outcomes will be interval censored. For participants lost to follow-up, we will look for surrogate outcome measures in the EHR; otherwise, they will be censored at their last monthly outcome assessment provided. Multiple imputation methods may be employed for time-varying covariate data if data are missing at random or completely at random (MAR/MCAR). Mixed models for continuous outcomes use all available data and can incorporate imputed missing covariates as appropriate. Similarly for frailty models for assessing risk or incidence rates.

REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

32 INFORMED CONSENT PROCESS

32.1.1 Consent/Assent Procedures and Documentation.

The consent process will take place in the hospital setting for patients (potential participants). Patients will be approached by study assessment staff and asked if they are interested in learning more about the THRIVE study. If they agree, then study assessment staff will provide the study flyer and will describe the study. If interested in participating, study assessment staff will screen patients using a study tablet at bedside. These potential participants will be assured that their participation in the THRIVE study is totally separate from their clinical care. Choosing or not choosing to participate in the study will not influence the type of care they receive. They will be given sufficient time to think about participation and ask questions clarifying the study. Study assessment staff will offer to have potential participants sign at the initial time of consent or will offer that they can return later to see if subjects are interested. Participants will be given sufficient time to ask questions. Participants will be asked to summarize the core components of the study prior to signing the consent form to confirm understanding. Once determined eligible to participate, participants will then receive the informed consent document and will sign consent for participation using e-consent.

Prior to starting each visit and delivering the intervention content, the THRIVE peer support specialists will confirm participants still wish to participate in THRIVE.

At conclusion of the patient enrollment, we will distribute an anonymous electronic survey to healthcare providers serving each of the clinical settings used for recruitment. Healthcare providers will be asked to complete informed consent electronically prior to completing the survey.

32.1.2 Consent of Participants who are, or become, decisionally impaired

Adults unable to provide consent are excluded from enrolling in the protocol. However, it is possible that participants enrolled in the protocol may permanently lose the capacity to consent for themselves during the course of this study. In the event this occurs, the subjects will be withdrawn from the study at the Principal Investigator's determination.

33 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification documenting the reason for study suspension or termination will be provided by the suspending or terminating party to study participants, investigators, funding agencies, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor/funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit/assessment schedule.

Circumstances that may warrant termination or suspension include, but are not limited to: determination of unexpected, significant, or unacceptable risk to participants; demonstration of efficacy that would warrant stopping; insufficient compliance of study staff to the protocol (i.e., significant protocol violations); data that are not sufficiently complete and/or evaluable; determination that the primary endpoint has been met; and/or determination of futility.

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, IRB, or other relevant regulatory or oversight bodies (OHRP, DSMB).

34 CONFIDENTIALITY AND PRIVACY

Protecting the rights and privacy of research participants will be the highest priority. The investigators and affiliated research institutions acknowledge the obligation to protect participants' confidentiality. This proposed project will engage in data sharing without confidentiality compromise using standard NIH approved mechanisms. Investigators will consider possible restrictions from local, State, Federal laws (e.g., HIPAA), and proprietary information or patent issues. Appropriate restrictions will be specified in data sharing plans that are developed as required. The precise content of the data sharing plan will vary depending on the data being collected and will specify: (i) Schedule for data sharing (data sharing will be timely and no later than one year from completion of quality assurance review of data), (ii) Format of final dataset, (iii) Documentation to be provided, (iv) Analytical tools to be provided, if any, (v) Need for data sharing agreement, and (vi) Mode of data sharing. Data collected by the study will be de-identified and anonymized before sharing to prevent linkage to individual research participants. This includes removal of all Personal Health Information (PHI), and indirect identifiers that are not listed as PHI, but could lead to "deductive disclosure," such as comment fields and site numbers. Study specific de-identification methods will be documented.

34.1.1 Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies

We will take all appropriate steps to ensure that we adhere to NIH's policy on dissemination of NIH-funded clinical trial information by addressing the following:

1. Registering the trial with ClinicalTrials.gov within 21 calendar days of enrollment of the first participant in the pilot trial.
2. Submitting trial results no later than one year following the completion date of the study. Our anticipated completion date for data collection is 08/31/2027. We anticipate that the primary analyses will be completed by 2/1/2028, at which time the primary analyses will be submitted as required (and within the one year required window by 8/31/2028).
3. Including a statement in our informed consent document that explains that this clinical trial is registered with ClinicialTrials.gov and that the results of the study (not including any identifying information) will be reported in accordance with the NIH dissemination policy for clinical trials.
4. Working with the University of Pittsburgh's Office for ClinicalTrials.gov to ensure that all requirements within the policy are adhered to in a timely fashion. The University of Pittsburgh is committed to complying with all policy requirements including registration and results reporting; the formal compliance statement can be located here: http://rcco.pitt.edu/clinicaltrialsgov.
5. We will employ several additional strategies to ensure local, regional, and national dissemination of findings. Our Community Advisory Board will serve as an important channel for dissemination. As a community-engaged study, we will ensure that study findings are communicated back to all parties and feedback from all partners will be sought throughout the project.

6. We will additionally submit abstracts to national scientific conferences and submit manuscripts for publication as outlined in the research and training plans.

34.1.2 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). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the protocol is managed in compliance with Federal statutes, and regulations. 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.

35 Future Use of Stored Specimens and Data

Not applicable.

36 Safety Oversight

Dr. Wilson will assume primary responsibility for overseeing all data and safety monitoring functions to ensure the safety of participants in the research proposed in this application, and to ensure the validity and integrity of the data obtained in this study. She will also regularly meet with the Co-Investigators and staff to track study progress and review these monitoring procedures. The investigative team will regularly oversee all aspects of the study, including participant recruitment, informed consent, data collection, data management and data analysis procedures, and will regularly assess the risk/benefit ratio associated with participation in the study.

Data and Safety Monitoring Board (DSMB)

The DSMB will be comprised of at least four members, one of whom will be a biostatistician. Other members will include an addiction expert and an infectious disease expert who have experience with behavioral clinical trials.

Reports: Dr. Murray-Krezan along with Dr. Wilson will prepare DSMB reports on a schedule specified in the DSMB Charter summarizing the status of study to date, demographic characteristics of participants obtained at the time of their study intake, any quality assurance and regulatory issues to date, as well as any AEs SAEs or protocol deviations to date. This report will also include a description of any reports published during the conduct of this study that are of relevance to the study. Information on the meetings will be provided to NIDA in annual progress reports. As with DSMB standards, the responsibilities of the DSMB include the following:

- Review and approve final study protocol and all associated materials
- Review interim data for appraisal of study-related adverse events
- Inspect interim and/or cumulative reports for data quality and completeness
- Evaluate the performance of individual sites (defined as one of three hospitals) according to proposed study milestones
- Evaluate compliance with recruitment and retention guidelines set forth by the study
- Guide study adherence to proposed protocol
- Review unanticipated and anticipated adverse study-related events or occurrences that may
- compromise confidentiality of study data

- Review any ethical considerations that may arise during the course of the study
- Make all associated recommendations for study improvement to the PI and investigative team in a timely fashion

As with standard DSMB guidelines, a chair will be selected prior to the start of recruitment, and this member will lead meetings and calls throughout the duration of the study. The board will meet initially to adopt a DSMB Charter and to discuss the protocol methodology, establish procedural guidelines, determine meeting frequency, and to come to a consensus on and approve a final protocol. After this initial approval, enrollment may begin. Subsequently, the board will schedule periodic meetings, which may convene as conference calls at the discretion of the board chair. There will be no less than one convened meeting per study year to review study progress and metrics as described above. Unscheduled meetings may be called by the chair in the event of an emergency or unanticipated SAE as reported by PI, statistical team, or review board. All board meetings will be closed to the public to protect confidential patient data. Notes from proceedings will be distributed to the investigative team members as soon as possible. The principal investigator will submit a summary of each DSMB meeting to the Project Officer and will be including these summaries in annual reports submitting to IRB as part of the continuing review process.

37 CLINICAL MONITORING

The DCC will utilize a centralized remote monitoring approach. Electronic consent and direct data entry into the electronic data management system (eSYSDM) allows the DCC to monitor data in real time. Monthly data reports generated by the DCC will be utilized by the monitoring team to conduct ongoing assessments of the quality of clinical trial data. The DCC Principal Investigator, data coordinator, and statistician will actively collaborate to monitor all study activities. Safeguards and alerts are strategically programmed into the eSYSDM to assist in these monitoring efforts. The DCC will generate reports focused on fields related to the data collected that establish inclusion criteria, exclusion criteria, primary and secondary outcomes, study endpoints, SAEs, missing information, and protocol deviations. Reports will be provided to and discussed with study investigators and coordinators during regularly scheduled teleconferences during the course of the trial.

38 QUALITY ASSURANCE AND QUALITY CONTROL

The Center for Biostatistics & Qualitative Methodology's Data Coordinating Center (CBQM DCC) at the University of Pittsburgh will be responsible for tracking data quality throughout the course of the study. Reports indicating data discrepancies or missingness will be disseminated to study staff for resolution.

Quality control (QC) procedures will be implemented as follows:

Informed consent --- QC staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data --- Data will be directly captured on in the electronic data capture system (eSYSDM), managed by the DCC (see **Data Handling and Record Keeping**).

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Interventionist Training and Tracking**.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

39 DATA HANDLING AND RECORD KEEPING

39.1.1 Data Collection and Management Responsibilities

The University of Pittsburgh's Center for Biostatistics & Qualitative Methodology's Data Coordinating Center (CBQM DCC) will function as the Data Coordinating Center (DCC) for the THRIVE study and will oversee all aspects of data management and quality review. Analyses and reports from the study data will be generated by the study statistician at the DCC. Electronic Case Report Forms (eCRF) will be created for use in a customized web application (eSYSDM) designed to meet the protocol requirements. The web application allows secured user-specific access to the eCRFs. Menus and reporting screens allow users to randomize, track, and enter data. The website will also act as a repository for THRIVE study-related documents including the Manual of Procedures (MOP), current protocol version, and additional general study information to keep sites updated on THRIVE progress. Printable hard-copy versions of these forms will be available on the website in case of problems with the electronic system.

All data obtained from participants during the screening process and during the course of the study will be kept confidential and will be filed by identification number. All study staff will be trained on these procedures in compliance with University of Pittsburgh and Pennsylvania procedures. Only project personnel will have access to signed consent forms, EHR data, and any other forms with individually identifying information. The central document linking participants' names and identification numbers will be destroyed as soon as the project has been completed per University policies. Structured assessments, chart review, and qualitative interviews will be conducted by trained research staff members in a private room or by phone in a secure site and directly entered into the eSYSDM. In the event that any back-up paper source documents must be collected (e.g., in the event of server downtime), these documents will be stored in a double-locked space (e.g., in a locked file cabinet within a locked office) that is accessible only to study staff. All data transmission and management will be fully encrypted. Audio recordings taken for fidelity monitoring purposes will not be associated with participant name or study ID. Recordings will be captured on dedicated USB recording devices. Peer support specialists will keep audio recording devices with them at all times when in use and store them in a locked cabinet in a locked office when not in use. Recordings will be uploaded to an encrypted location to be shared with the principal investigator for review and then immediately destroyed after the review has been completed. Devices to be used to collect data will be password-protected. All electronic data will be stored in encrypted form behind the University of Pittsburgh's firewall on their servers A participant tracking form that includes participant information for tracking and scheduling follow up assessments will be used only by study staff; this form will be stored separately from other personal data. Data files will be exported from the server and saved on a secured network drive managed by University of Pennsylvania or University of Pittsburgh's IT Department.

Study Records Retention

All participants will be assigned a unique alphanumeric study identification number upon enrollment. This number will be used to identify all study data forms, EHR data, digital audio-recordings (or qualitative interviews), transcripts, and other research instruments. No other information that would disclose a participant's identity will appear on any research instruments, notes, or in the transcripts of qualitative interviews.

A master index file that links participants' names and identifying information with participants' identification numbers will be stored in electronic form that is accessible only to study staff.

As part of the informed consent process, participants will be informed that all information they provide in structured assessments and qualitative interviews is confidential with the following exceptions: (1) if they

are in imminent danger of seriously harming themselves or another person, the appropriate authorities will be contacted; and (2) if they report the physical or sexual abuse of another person under the age of 18, the appropriate agencies will be contacted.

All publications and presentations based on study data will report aggregate findings only and, when reporting qualitative interview data, pseudonyms will be used and any other information that could potentially identify a participant or any other individual will be redacted.

40 PROTOCOL DEVIATIONS AND NON-COMPLIANCE

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations and/or non-compliance to the NIH Institutional Review Board as per Policy 801. All deviations must be addressed in study source documents, reported to the NIH Program Official and NIDA. The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

40.1.1.1 NIH Definition of Protocol Deviation

A protocol deviation is any changed, divergence, or departure from the IRB-approved research protocol.

- Major deviations: Deviations from the IRB approved protocol that have, or may have the potential to, negatively impact the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.
- Minor deviations: Deviations that do not have the potential to negatively impact the rights, safety or welfare of subjects or others, or the scientific integrity or validity of the study.

41 HUMAN DATA SHARING, INCLUDING GENOMIC DATA SHARING, AND PUBLICATION

It is understood that scientific research depends on unhindered information flow and future research must be able to build on previous efforts and discoveries. NIH policy requires research data, especially unique data, from NIH-supported research to be made available to other investigators. This includes data from basic research, clinical studies, surveys, and other types of research; some of which will be encompassed by this proposal. Data collected through the proposed studies includes both qualitative data and quantitative survey and self-reported outcomes, and data obtained from the electronic health record. Data will be collected to conform with the Findable, Accessible, Interoperable, and Reusable (FAIR) principles. No data will be collected prior to approval of the protocol at the University of Pittsburgh IRB.

Data collected from this study will be submitted to study appropriate, domain-specific, or generalist repositories in consultation with the HEAL Data Stewardship Group to ensure the data will be accessible via the HEAL Initiative Data Ecosystem. We will ensure that data is prepared for storage using minimal metadata standards and the use of core HEAL Clinical Data Elements as appropriate. Tools (data, software, libraries, research tools, etc.) will be made available, in accordance with the Final NIH Statement on Sharing Research Data to all researchers in both the private and public sector free or for a nominal charge and with minimal restriction.

41.1.1 NIH Data Management and Sharing Policy and NIH Genomic Data Sharing Policy Compliance

This study will comply with the NIH Data Management and Sharing (DMS) Policy, which applies to all new and ongoing NIH-funded research in the IRP, as of January 25, 2023, that is associated with a ZIA, with a clinical protocol that undergoes scientific review and/or will involve genomic data sharing.

41.1.2 NIH Public Access Policy Compliance

This study will be in compliance with the NIH Public Access Policy. Manuscripts will be submitted to PubMed Central (PMC) upon acceptance for publication and no later than 12 months after the official

date of publication. We will include the PMC Central ID (PMCID) when citing applicable articles in NIH applications, proposals, and reports.

42 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership, in conjunction with the NIH, has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest. All study investigators and staff will be required to follow the conflict of interest policy instituted by their university of record.

ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means

MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

REFERENCES

1. Harm Reduction Principles. National Harm Reduction Coalition. Accessed September 9, 2022. https://harmreduction.org/about-us/principles-of-harm-reduction/

2. Friedman SR, de Jong W, Rossi D, et al. Harm reduction theory: Users' culture, micro-social indigenous health promotion, and the self-organization and outside-organizing of users' groups. *Int J Drug Policy*. 2007;18(2):107-117. doi:10.1016/j.drugpo.2006.11.006

3. Pauly B (Bernie), Reist D, Belle-Isle L, Schactman C. Housing and health promotion: What is the role of health promotion in addressing homelessness? *Int J Drug Policy*. 2013;24(4):284-290. doi:10.1016/j.drugpo.2013.03.008

4. Pauly B, Wallace B, Barber K. Turning a blind eye: implementation of health promotion in a transitional programme setting. *Drugs Educ Prev Policy*. 2018;25(1):21-30. doi:10.1080/09687637.2017.1337081

5. Pauly B. Harm reduction through a social justice lens. *Int J Drug Policy*. 2008;19(1):4-10. doi:10.1016/j.drugpo.2007.11.005

6. Stein MD, Phillips KT, Herman DS, et al. Skin-cleaning among hospitalized people who inject drugs: a randomized controlled trial. *Addiction*. 2021;116(5):1122-1130. doi:10.1111/add.15236

7. Phillips KT, Stewart C, Anderson BJ, Liebschutz JM, Herman DS, Stein MD. A randomized controlled trial of a brief behavioral intervention to reduce skin and soft tissue infections among people who inject drugs. *Drug Alcohol Depend*. 2021;221:108646. doi:10.1016/j.drugalcdep.2021.108646

8. Moustaqim-Barrette A, Dhillon D, Ng J, et al. Take-home naloxone programs for suspected opioid overdose in community settings: a scoping umbrella review. *BMC Public Health*. 2021;21(1):597. doi:10.1186/s12889-021-10497-2

9. McDonald R, Strang J. Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. *Addiction*. 2016;111(7):1177-1187. doi:10.1111/add.13326

10. Krieger MS, Yedinak JL, Buxton JA, et al. High willingness to use rapid fentanyl test strips among young adults who use drugs. *Harm Reduct J*. 2018;15(1):7. doi:10.1186/s12954-018-0213-2

11. Sherman SG, Morales KB, Park JN, McKenzie M, Marshall BDL, Green TC. Acceptability of implementing community-based drug checking services for people who use drugs in three United States cities: Baltimore, Boston and Providence. *Int J Drug Policy*. 2019;68:46-53. doi:10.1016/j.drugpo.2019.03.003

12. Goldman JE, Waye KM, Periera KA, Krieger MS, Yedinak JL, Marshall BDL. Perspectives on rapid fentanyl test strips as a health promotion practice among young adults who use drugs: a qualitative study. *Harm Reduct J*. 2019;16(1):3. doi:10.1186/s12954-018-0276-0

13. Peiper NC, Clarke SD, Vincent LB, Ciccarone D, Kral AH, Zibbell JE. Fentanyl test strips as an opioid overdose prevention strategy: Findings from a syringe services program in the Southeastern United States. *Int J Drug Policy*. 2019;63:122-128. doi:10.1016/j.drugpo.2018.08.007

14. Hawk M, Coulter RWS, Egan JE, et al. Harm reduction principles for healthcare settings. *Harm Reduct J*. 2017;14(1):70. doi:10.1186/s12954-017-0196-4

15. Chan CA, Canver B, McNeil R, Sue KL. Harm Reduction in Health Care Settings. *Med Clin North Am*. 2022;106(1):201-217. doi:10.1016/j.mcna.2021.09.002

16. Wilson JD, Berk J, Adger H, Feldman L. Identifying Missed Clinical Opportunities in Delivery of Overdose Prevention and Naloxone Prescription to Adolescents Using Opioids. *J Adolesc Health*. 2018;63(2):245-248. doi:10.1016/j.jadohealth.2018.05.011

17. Wilson JD, Spicyn N, Matson P, Alvanzo A, Feldman L. Internal medicine resident knowledge, attitudes, and barriers to naloxone prescription in hospital and clinic settings. *Subst Abuse*. 2016;37(3):480-487. doi:10.1080/08897077.2016.1142921

18. Wilson JD, Berk J, Matson P, et al. A Cross-sectional Survey Using Clinical Vignettes to Examine Overdose Risk Assessment and Willingness to Prescribe Naloxone. *J Gen Intern Med*. 2019;34(4):507-509. doi:10.1007/s11606-018-4733-y

19. Macalino G, Sachdev DD, Rich J, et al. A national physician survey on prescribing syringes as an HIV prevention measure. *Subst Abuse Treat Prev Policy*. 2009;4(1):13. doi:10.1186/1747-597X-4-13

20. Stack E, Hildebran C, Leichtling G, et al. Peer Recovery Support Services Across the Continuum: In Community, Hospital, Corrections, and Treatment and Recovery Agency Settings – A Narrative Review. *J Addict Med*. 2022;16(1):93-100. doi:10.1097/ADM.0000000000000810

21. Mercer F, Miler JA, Pauly B, et al. Peer Support and Overdose Prevention Responses: A Systematic 'State-of-the-Art' Review. *Int J Environ Res Public Health*. 2021;18(22):12073. doi:10.3390/ijerph182212073

22. Kennedy MC, Boyd J, Mayer S, Collins A, Kerr T, McNeil R. Peer worker involvement in low-threshold supervised consumption facilities in the context of an overdose epidemic in Vancouver, Canada. *Soc Sci Med*. 2019;225:60-68. doi:10.1016/j.socscimed.2019.02.014

23. Owczarzak J, Weicker N, Urquhart G, Morris M, Park JN, Sherman SG. "We know the streets:" race, place, and the politics of health promotion. *Health Place*. 2020;64:102376. doi:10.1016/j.healthplace.2020.102376

24. Bardwell G, Kerr T, Boyd J, McNeil R. Characterizing peer roles in an overdose crisis: Preferences for peer workers in overdose response programs in emergency shelters. *Drug Alcohol Depend*. 2018;190:6-8. doi:10.1016/j.drugalcdep.2018.05.023

25. Pauly B, Wallace B, Pagan F, et al. Impact of overdose prevention sites during a public health emergency in Victoria, Canada. Panagiotoglou D, ed. *PLOS ONE*. 2020;15(5):e0229208. doi:10.1371/journal.pone.0229208

26. Small W, Wood E, Tobin D, Rikley J, Lapushinsky D, Kerr T. The Injection Support Team: A Peer-Driven Program to Address Unsafe Injecting in a Canadian Setting. *Subst Use Misuse*. 2012;47(5):491-501. doi:10.3109/10826084.2012.644107

27. Hayashi K, Wood E, Wiebe L, Qi J, Kerr T. An external evaluation of a peer-run outreach-based syringe exchange in Vancouver, Canada. *Int J Drug Policy*. 2010;21(5):418-421. doi:10.1016/j.drugpo.2010.03.002

28. Dechman MK. Peer helpers' struggles to care for "others" who inject drugs. *Int J Drug Policy*. 2015;26(5):492-500. doi:10.1016/j.drugpo.2014.12.010

29. Marshall C, Perreault M, Archambault L, Milton D. Experiences of peer-trainers in a take-home naloxone program: Results from a qualitative study. *Int J Drug Policy*. 2017;41:19-28. doi:10.1016/j.drugpo.2016.11.015

30. Callon C, Charles G, Alexander R, Small W, Kerr T. 'On the same level': facilitators' experiences running a drug user-led safer injecting education campaign. *Harm Reduct J*. 2013;10(1):4. doi:10.1186/1477-7517-10-4

31. ColÓn RM, Deren S, Guarino H, Mino M, Kang SY. Challenges in Recruiting and Training Drug Treatment Patients as Peer Outreach Workers: A Perspective From the Field. *Subst Use Misuse*. 2010;45(12):1892-1908. doi:10.3109/10826081003684863

32. Newland J, Treloar C. Peer education for people who inject drugs in New South Wales: Advantages, unanticipated benefits and challenges. *Drugs Educ Prev Policy*. 2013;20(4):304-311. doi:10.3109/09687637.2012.761951

33. Hay B, Henderson C, Maltby J, Canales JJ. Influence of Peer-Based Needle Exchange Programs on Mental Health Status in People Who Inject Drugs: A Nationwide New Zealand Study. *Front Psychiatry*. 2017;7. doi:10.3389/fpsyt.2016.00211

34. Cacari-Stone L, Wallerstein N, Garcia AP, Minkler M. The Promise of Community-Based Participatory Research for Health Equity: A Conceptual Model for Bridging Evidence With Policy. *Am J Public Health*. 2014;104(9):1615-1623. doi:10.2105/AJPH.2014.301961

35. Adams SA, Heiney SP, Brandt HM, et al. A Comparison of a Centralized Versus De-centralized Recruitment Schema in Two Community-Based Participatory Research Studies for Cancer Prevention. *J Community Health*. 2015;40(2):251-259. doi:10.1007/s10900-014-9924-9

36. Burke JG, Jones J, Yonas M, et al. PCOR, CER, and CBPR: Alphabet Soup or Complementary Fields of Health Research?: Stakeholder-Engaged Research. *Clin Transl Sci*. 2013;6(6):493-496. doi:10.1111/cts.12064

37. Horowitz CR, Brenner BL, Lachapelle S, Amara DA, Arniella G. Effective Recruitment of Minority Populations Through Community-Led Strategies. *Am J Prev Med*. 2009;37(6):S195-S200. doi:10.1016/j.amepre.2009.08.006

38. Wilson JD, Altieri Dunn SC, Roy P, Joseph E, Klipp S, Liebschutz J. Inpatient Addiction Medicine Consultation Service Impact on Post-discharge Patient Mortality: a Propensity-Matched Analysis. *J Gen Intern Med*. 2022;37(10):2521-2525. doi:10.1007/s11606-021-07362-8

39. Ojo SO, Bailey DP, Hewson DJ, Chater AM. Perceived Barriers and Facilitators to Breaking Up Sitting Time among Desk-Based Office Workers: A Qualitative Investigation Using the TDF and COM-B. *Int J Environ Res Public Health*. 2019;16(16):2903. doi:10.3390/ijerph16162903

40. McDonagh LK, Saunders JM, Cassell J, et al. Application of the COM-B model to barriers and facilitators to chlamydia testing in general practice for young people and primary care practitioners: a systematic review. *Implement Sci*. 2018;13(1):130. doi:10.1186/s13012-018-0821-y

41. Timlin D, McCormack JM, Simpson EE. Using the COM-B model to identify barriers and facilitators towards adoption of a diet associated with cognitive function (MIND diet). *Public Health Nutr*. 2021;24(7):1657-1670. doi:10.1017/S1368980020001445

42. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. *Med Care*. 2012;50(3):217-226. doi:10.1097/MLR.0b013e3182408812

43. Binswanger IA, Kral AH, Bluthenthal RN, Rybold DJ, Edlin BR. High prevalence of abscesses and cellulitis among community-recruited injection drug users in San Francisco. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2000;30(3):579-581. doi:10.1086/313703

44. Fink DS, Lindsay SP, Slymen DJ, Kral AH, Bluthenthal RN. Abscess and self-treatment among injection drug users at four California syringe exchanges and their surrounding communities. *Subst Use Misuse*. 2013;48(7):523-531. doi:10.3109/10826084.2013.787094

45. Shrestha S, Stopka TJ, Hughto JMW, et al. Prevalence and correlates of non-fatal overdose among people who use drugs: findings from rapid assessments in Massachusetts, 2017-2019. *Harm Reduct J*. 2021;18(1):93. doi:10.1186/s12954-021-00538-9

46. Stensrud MJ, Hernán MA. Why Test for Proportional Hazards? *JAMA*. 2020;323(14):1401-1402. doi:10.1001/jama.2020.1267

47. Bradburn MJ, Clark TG, Love SB, Altman DG. Survival analysis Part III: multivariate data analysis -- choosing a model and assessing its adequacy and fit. *Br J Cancer*. 2003;89(4):605-611. doi:10.1038/sj.bjc.6601120