A Tailored, Peer-delivered Intervention to Reduce Recurring Opioid Overdoses

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A Tailored, Peer-delivered Intervention to Reduce Recurring Opioid Overdoses

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A. SPECIFIC AIMS

Recurring opioid overdose (OOD) is a significant problem in the U.S. The only completely effective method of preventing subsequent OOD is successful treatment of the underlying opioid use disorder (OUD). Despite this, there are no interventions to facilitate treatment entry for patients experiencing a non-fatal OOD. This project will further develop and test the Tailored Telephone Intervention delivered by Peers to Prevent Recurring Opioid Overdoses (TTIP-PRO), a promising, low-cost, intervention to facilitate entry into medication assisted treatment (MAT) for individuals experiencing a non-fatal OOD.

The specific aims of this project are to:

1) Finalize the Peer Interventionist training materials by creating training files and evaluating the inter-rater reliability of TTIP-PRO's competence assessment; and

2) Conduct pilot testing in preparation for a full-scale clinical trial

Exploratory aims are to:

E1) Test the validity of two assessments developed for TTIP-PRO;

E2) Test our conceptual model of TTIP-PRO's mechanisms of change.

B. BACKGROUND AND SIGNIFICANCE

In recent years, the U.S. has experienced a growing opioid-use epidemic accompanied by a dramatic rise in OOD deaths.[1-3] In 2012, prescription opioids were involved in 16,000 overdose deaths, while heroin was involved in 5,925 overdose deaths; this equates to an average of 60 deaths per day.[4] Non-fatal OODs have also drastically increased in recent years. In 2011, there were 420,000 emergency department (ED) visits related to abuse of prescription opioids, representing an increase of over 150% since 2004. In the same year, there were 258,482 ED visits for heroin use,[5] resulting in a combined average of over 1,800 opioid-abuse-related ED visits per day. In addition to the human cost of OODs, there are significant financial costs as well: the median cost of treatment was $4,521 for non-hospitalized, and $22,460 for hospitalized, OOD patients.[6]

Individuals experiencing a non-fatal OOD are at heightened risk for future OODs.[7-10] A recent study revealed that 7% of all patients who were treated for an OOD in an ED were treated for more than one OOD within a single year.[6] The proportion of patients with more than one OOD was higher in particular subsamples, with 31% of Medicare and 25% of Medicaid OOD patients having more than one OOD ED visit in one year.[6] Patients with repeated OODs accounted for 15% of all OOD ED visits and were more likely to be hospitalized.[6] Attempts to mitigate OOD deaths have largely focused on naloxone, an opioid antagonist that is effective in OOD reversal. Specifically, there have been concerted efforts to increase the accessibility of naloxone [3] and to train opioid-abusing individuals and their families on the signs of OOD and naloxone administration.[11-14] Although naloxone can reverse an acute overdose there is no guarantee that it will be available in time. The only completely effective method for preventing subsequent OOD is successful treatment of the underlying opioid use disorder (OUD). Receiving medication assisted treatment (MAT) for OUD (e.g., methadone- or buprenorphine-maintenance) significantly reduces the likelihood of OOD.[15-18] However, in addition to the barriers of waiting lists and the costs of MAT, inaccurate perceptions of MAT – including myths about its side effects and lack of efficacy – also prevent some individuals with OUD from entering treatment.[19, 20] Currently there are no published secondary prevention interventions to help patients who have experienced a non-fatal OOD enter OUD treatment.

A primary goal of TTIP-PRO is to address negative, inaccurate perceptions of MAT in order to encourage individuals with OUD to enter a MAT program. Research suggests that individuals experiencing a recent non-fatal OOD may be amenable to entering treatment.[21] Specifically, 26% of injection drug users experiencing a non-fatal OOD sought treatment for their addiction within 30 days of the event and 75% of those patients enrolled in treatment.[21] Seeking treatment was significantly more likely when someone spoke to the patient about addiction treatment.[21] Thus, engaging individuals with a relatively recent OOD in a MAT program should be an achievable goal. In addition to using MAT to reduce OOD risk, it has been proposed that educating opioid abusers about OOD risk factors could reduce OOD rates.[17, 22] While several studies have demonstrated that education can significantly increase knowledge,[23, 24] the impact on risk reduction behavior is typically not assessed. [25] In addition, there can be a disconnect between knowledge and behavior, with individuals knowingly engaging in behaviors that can increase OOD risk.[26]

In order to maximize the potential impact of TTIP-PRO on risk reduction behavior, particularly on entering a MAT program, the creation of TTIP-PRO was guided by the elaboration likelihood model (ELM) of persuasion.[27, 28] The ELM posits that people process persuasive information through two routes: central, in which the material is actively considered, and peripheral, in which the material is given only superficial consideration. Information that is processed centrally and found to be convincing and valuable results in a positive attitude change that is relatively long lasting and predictive of behavior. Communication that is processed by the peripheral route results in attitudes that are susceptible to further change and not predictive of behavior. Conditions that increase the likelihood of information being centrally processed and leading to a positive attitude change (e.g., that MAT would be beneficial) include: 1) the material is seen as personally relevant; 2) the information can be readily understood; and 3) the source of the information is considered credible. TTIP-PRO was designed to maximize each of these conditions.

1) Personally Relevant: Research suggests that the individuals targeted in TTIP-PRO, that is, those recently experiencing an OOD, are more likely to find information about OOD and the benefits of MAT personally relevant compared to individuals with OUD who have not recently overdosed. McGregor and colleagues[17] found that a significantly greater proportion of individuals experiencing an OOD within the prior 6 months estimated that a future OOD was likely (56%) compared to those who had experienced an OOD more than 6 months ago (16%) and to individuals with OUD who had never experienced an OOD (14%). In applying ELM to health promotion messages, a key recommendation is to use tailored messaging to increase the relevance of the information to intervention recipients.[29] Thus, TTIP-PRO provides tailored feedback to a given individual based on his/her OOD risk factors and knowledge about OOD and MAT. 2) Easy to Understand: To enhance patients' understanding of the information provided in TTIP-PRO, information is provided both verbally and in writing to facilitate multimodal learning. The verbal component helps ensure that low literacy is not a barrier to understanding, as does careful attention to reading level for the written component. 3) Credible: To provide a credible source of information, all information has a solid empirical basis and is delivered by a peer interventionist, who has personal experience with OUD and OOD. Peer interventionists are typically perceived as highly credible and can provide personal knowledge that facilitates active learning through a shared experiential process.[30]

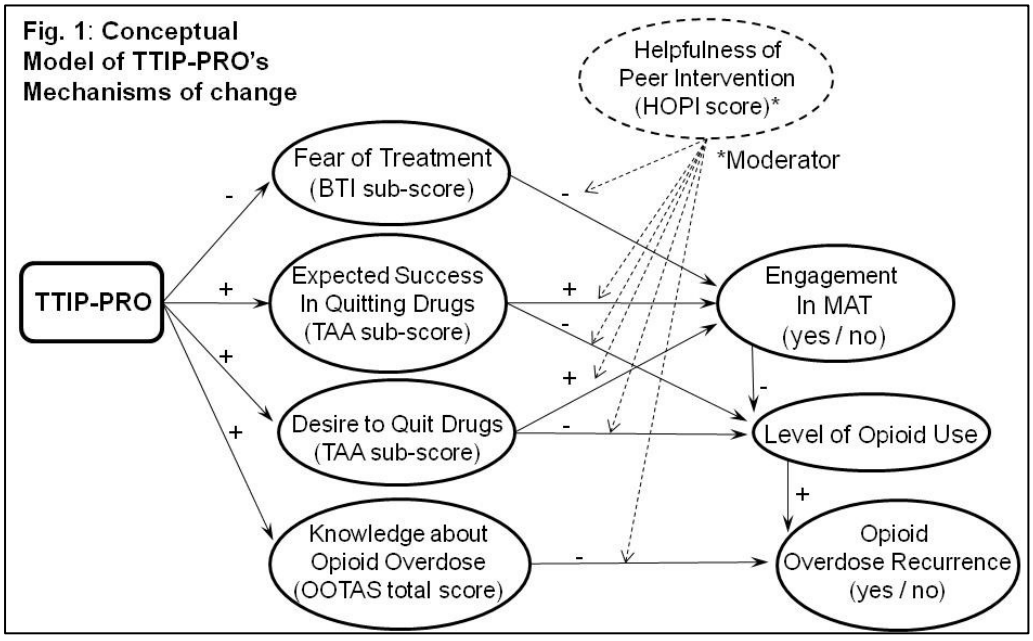
Our conceptual model of TTIP-PRO's mechanisms of change is provided in **Fig.1**. The measures for the four hypothesized mediators (i.e., fear of treatment, self-efficacy for quitting, desire to quit using drugs, and knowledge about OOD) can be found in section 1.4 (study assessments). According to ELM, information will be processed centrally, and have the most impact, to the degree that the information is seen as personally relevant and from a credible source; our measure of this, the Helpfulness of Peer Intervention (HOPI) is described in section 1.4 (study assessments); we hypothesize that the HOPI score will be a moderator of the mediator-outcome relationships.

C. PRELIMINARY STUDIES

Our development and initial testing of the TTIP-PRO intervention is described by Winhusen et al.[31] In brief, we conducted a pre-post study to assess TTIP-PRO-content acceptability and software performance. Two Peer Interventionists, who were abstinent from illicit opioids, enrolled in MAT at the UC Addiction Sciences Division (ASD) program, and had experience with OOD, were enrolled and trained to provide the TTIP-PRO intervention. Recruitment letters were sent to patients treated for OOD at the University of Cincinnati Medical Center (UCMC) emergency department (ED) within the prior 8 months. Eight patients received TTIP-PRO and completed pre/post assessment. Peer Interventionists reported high satisfaction with TTIP-PRO. There were no performance issues with the TTIP-PRO-software. All participants rated TTIP-PRO as "very helpful" and their OOD knowledge increased significantly, with 69.9% correct responses pre-TTIP-PRO and 93.6% post-TTIP-PRO.

D. INVESTIGATOR EXPERIENCE

Drs. Winhusen, Lyons, and Wilder worked together on the initial testing of TTIP-PRO.[31] Drs. Winhusen and Lyons were site co-investigators for a prior clinical trial that tested screening, brief intervention, referral, and treatment (SBIRT) in the ED and participants were followed up for 12 months (NIDA's Clinical Trials Network SMART-ED trial[32]). Dr. Winhusen is a licensed clinical psychologist and one of the foremost experts in conducting multi-site addiction clinical trials in clinical practice settings. Specifically, Dr. Winhusen has been the national PI of five[33-37], and Co-PI of a sixth[38], multi-site trials in NIDA's Clinical Trials network (CTN) since 2001. Within the past five years, Dr. Winhusen has overseen the successful implementation of 13 clinical trials at 7 community treatment sites, located in 5 states. In addition to serving as a co-investigator for the NIDA CTN SMART-ED trial, Dr. Lyons helped to lead a successful CDC-funded randomized trial of a brief-intervention to prevent risky driving and drinking practices in ED patients.[39] Dr. Wilder is a board-certified addiction psychiatrist with expertise in opioid overdose prevention via naloxone distribution to patients in OUD treatment. She helped develop the Cincinnati VA Overdose Education and Naloxone Distribution (OEND) Program. Additionally, Dr. Wilder has previous experience in the development and dissemination of peer interventions, specifically facilitation of psychiatric advance directives.[40] Dr. Wilder developed the initial peer training manual employed by the state of Virginia[41] and was instrumental in identifying barriers to implementation of the intervention.[42]



E. METHODS

1.0 Study Design

1.1 Overview of study design

Following finalization of the Peer Interventionist training materials (described below in section 3.0), a pilot efficacy trial will be completed. This pilot study is a randomized controlled intent-to-treat (ITT) clinical trial. Potential participants will be recruited through various methods, which include but are not limited to advertisements, flyers, and word-of-mouth. Approximately eighty eligible participants will be randomized in a 1:1 ratio to the control condition (Information and NARCAN® Nasal Spray kit) or to the experimental condition (TTIP-PRO in addition to the elements provided in the control condition). All participants will complete a follow-up phone call approximately 3-weeks post-randomization, during which process measures will be completed, and in-person visits at approximately 3, 6-, and 12-months following enrollment.

1.2 Number of sites and participants

This is a single site study; all data will be collected at the University of Cincinnati. This project includes two types of participants: 1) the participants who may receive the TTIP-PRO intervention, referred to as participants, and 2) the participants who will serve as Peer Interventionists. Participants will be recruited to develop training audio files until 4 training tapes are obtained; all of these "training" participants will receive the TTIP-PRO intervention. Approximately 80 participants will be randomized into the pilot efficacy trial. Approximately 15 Peer Interventionists will participate.

1.3 Study eligibility

This project includes two types of participants: 1) the participants who may receive the TTIP-PRO intervention, referred to as participants, and 2) the participants who will serve as Peer Interventionists.

1.3.1 Participants

All potential participants will be recruited through various methods, which include but are not limited to advertisements, flyers, and word-of-mouth. Eligible participants will meet all inclusion, and no exclusion criteria:

Inclusion Criteria:

1. Report having been treated for an OOD within the past 6 months;
2. Age 18 years or older;
3. Scores "high risk" for heroin and/or non-medical use of prescription opioids on the NIDA modified ASSIST (i.e., ≥ 27);
4. Be able to understand the study, and having understood, provide written informed consent in English;
5. Access to a phone (for TTIP-PRO intervention and phone follow-up);
6. Be willing to have their intervention audio recorded and rated if randomized to TTIP-PRO;
7. Have an opioid-positive baseline/screening urine drug screen.

Exclusion Criteria:

1. In the judgment of the investigator, would not be expected to complete the study protocol (e.g., due to relocation from the clinic area, probable incarceration, etc.)
2. Current engagement in addiction treatment;
3. Residence more than 40 miles from the location of follow-up visits;
4. Inability to provide sufficient contact information (must provide at least 2 reliable locators);
5. Prior participation in the current study.

1.3.2 Peer Interventionists

All potential Peer Interventionists will be recruited primarily by word of mouth from a UC ASD (UC Health/UCPC) MAT (i.e., receiving methadone or buprenorphine) clinic. For individuals early in recovery or struggling with recovery and/or other issues, interacting with active users could increase their risk of relapse. Our Peer Interventionist eligibility criteria are designed to select only those whose recovery is sufficiently stable to mitigate this risk.

Inclusion Criteria:

1. Age 18 years or older;
2. Enrolled in UC ASD (i.e., UC Health/UCPC) MAT program;
3. Enrolled in a MAT program for at least one year;
4. Report being abstinent from illicit opioids for at least one year;
5. Report having experienced, witnessed, and/or lost a family member or friend to an overdose.

Exclusion Criteria:

1. Unwilling to sign a release of information (ROI) to allow research staff to confirm pertinent eligibility criteria and to monitor clinical status with UC ASD (i.e., UC Health/UCPC) MAT clinical staff;
2. Clinical staff from their program have significant concerns about their participation;
3. Unwilling to have their sessions audio recorded and assessed by a TTIP-PRO trainer;
4. Specific plan to leave the UC ASD (i.e., UC Health/UCPC) MAT program within the next 6 months.

1.4 Study assessments

1.4.1 Participant Measures

Primary outcome measure. Entered MAT (Yes/No) – The determination of whether the participant enrolled in a MAT program within the 12-month follow-up will be based on participant self-report, confirmed by clinic records, obtained with the proper release of information (ROI) from the participant.

Secondary outcome measures. Opioid overdose (Yes/No)–Determination of whether the participant experiences an OOD within 12-month follow-up will be based on participant self-report.

Opioid use will be assessed with the Timeline Follow-back (TLFB) procedure[43, 44] and urine drug screens (UDS). At each assessment point, the TLFB will be used to assess self-reported substance use for the 28 days prior to the visit. The rapid UDS will include screens for substances of abuse. Urine samples will be collected using temperature monitoring and the validity of urine samples will be checked with the use of a commercially available adulterant test.

Process measures. Barriers to Treatment Inventory (BTI) - This 25-item Likert-scale questionnaire has seven internally consistent subscales relating to Absence of Problem, Negative Social Support, Fear of Treatment, Privacy Concerns, Time Conflict, Poor Treatment Availability, and Admission Difficulty.[45, 46] The Fear of Treatment subscale will be evaluated as a mediator of TTIP-PRO's efficacy (see ***Fig. 1***).

Thoughts about abstinence (TAA) - Participants' commitment to abstinence from illicit substances will be assessed with the TAA.[47] This measure assesses the participant's desire to quit, expected success in quitting and estimated difficulty in avoiding relapse. Both desire to quit and expected success in quitting will be evaluated as mediators (see ***Fig. 1***).

The Opioid Overdose and Treatment Awareness Survey (OOTAS). The OOTAS assesses knowledge about OOD and MAT and is comprised of four sections: 1) OOD risk factors; 2) signs of an OOD; 3) how to respond to an OOD; and 4) myths about MAT. The total OOTAS score will be evaluated as a mediator of TTIP-PRO's efficacy (see ***Fig. 1***).

The Helpfulness of Peer Intervention (HOPI) – The creation of TTIP-PRO was guided by the ELM which posits that material seen as personally relevant and from a credible source will be centrally processed, resulting in a positive attitude change that is relatively long lasting and predictive of behavior.[27, 28] Otherwise, the information will be processed by the peripheral route and will result in attitudes that are susceptible to further change and not predictive of behavior.[27, 28] Thus the degree to which the information provided in TTIP-PRO is seen as personally relevant and from a credible source will likely moderate the mediator-outcome relationship (see ***Fig. 1***). Because there are no published assessments of these qualities, we created the HOPI. The HOPI is a 12-item assessment in which each statement is rated on a 5-point Likert scale (1=strongly disagree; 5=strongly agree). TTIP-PRO is assessed on two subscales: 1) personally relevant and 2) credible. According to ELM,[27, 28] likability and credibility are the principal components of source credibility and so the credible subscale focuses on the participant's perceptions of the Peer Interventionist. The total HOPI score will be tested as a moderator of the mediator-outcome relationships (see ***Fig. 1***); two versions of the HOPI will be used – one for participants randomized to TTIP-PRO and one for those randomized to the control condition, which will assess the degree to which participants found the materials provided to be personally relevant and credible.

Other measures.

Demographics -This assessment includes questions about the participant's ethnicity, age, and sex.

The Personal Opioid-Overdose Risk Survey (PORS) The PORS assesses an individual's OOD risk factors. It only includes risk factors for which there is documented evidence and scoring for each item is based on the strength of the evidence that the factor increases risk.[31]

NARCAN® Nasal Spray kit Utilization - Determination of whether the participant utilizes the kit within 12-month follow-up will be based on participant self-report.

1.4.2 Peer Interventionist Assessments

Demographics -This assessment includes questions about the Peer Interventionist's ethnicity, age, and sex.

Peer Volunteer Experience Questionnaire (PVEQ) – The PVEQ was developed by Dennis and colleagues to obtain feedback from peer volunteers delivering an intervention for post-partum depression.[48] Three sections of the PVEQ are relevant for TTIP-PRO and will be used to obtain feedback on: 1) the training and certification process; 2) interactions with participants; and 3) the personal effects of being a Peer Interventionist (e.g., benefits and drawbacks of being a Peer Interventionist). An additional item will be included to assess the Peer Interventionist's satisfaction with his/her experience, rated on a 5-point scale (*1-very dissatisfied, 2-dissatisfied, 3-neither satisfied or dissatisfied, 4- satisfied, 5-very satisfied*).

Global Health will be assessed with the PROMIS 10-item measure for Global Health, which briefly but comprehensively assesses physical, mental, and social health; this is a reliable (Cronbach's $\alpha > 0.80$) measure with demonstrated construct validity.[49] The interventionists will complete this measure, used to assess positive and negative outcomes, prior to being assigned participants (baseline), every 4 months during the approximately 14 month enrollment period, and after the last TTIP-PRO intervention has been provided.

1.4.3 Collection and reporting of adverse events (AEs) and serious adverse events (SAEs)
In general, the risks associated with trials employing behavioral interventions are presumed minimal relative to those evaluating pharmacologic interventions. Based on the TTIP-PRO acceptability study the risk from TTIP-PRO is low.[31] Still, for the present trial, the population studied may possibly be at higher risk given the nature of the disorder and the population. Thus, the following events, which are not defined as SAEs, will be tracked on an AE CRF for participants and Peer Interventionists:

1. Suicidal ideation
2. Homicidal ideation

In addition, the following events will be tracked on an AE CRF for the Peer Interventionists:

1. Discharge from MAT program for any reason
2. Illicit opioid use
3. Other clinical deterioration as reported by clinic staff

For TTIP-PRO, which is a behavioral trial, the RA is primarily responsible for assessing the occurrence of AEs/SAEs with oversight by the Study Medical Monitor and PI. For Participants, the RA will query about how s/he has been feeling since the last visit (i.e., at the follow-up phone call in week 3 and in-person visits at 3, 6-, and 12-months following enrollment). For Peer Interventionists, the RA will query about how s/he has been feeling following the delivery of each TTIP-PRO intervention. All AEs/SAEs occurring during the course of the clinical trial will be collected, documented, and reported by the investigator or sub-investigators in accordance with reporting requirements. Dr. Lyons or the designated study physician will assess the severity, causality and outcome of all AEs and SAEs. It will also be Drs. Lyons', Winhusen's, and Wilder's responsibility to manage all AEs and SAEs and to make referrals for appropriate care, as necessary. All SAEs will be reported to the University of Cincinnati Institutional Review Board and the NIDA project officer within 72 hours of their discovery. All subject information will be de-identified when reporting serious adverse events.

1.5 Randomization Plan
Eligible participants will be randomized in a 1:1 ratio to the control or experimental arms. The randomization sequence will be unknown to the research staff.

2.0 Study Treatments

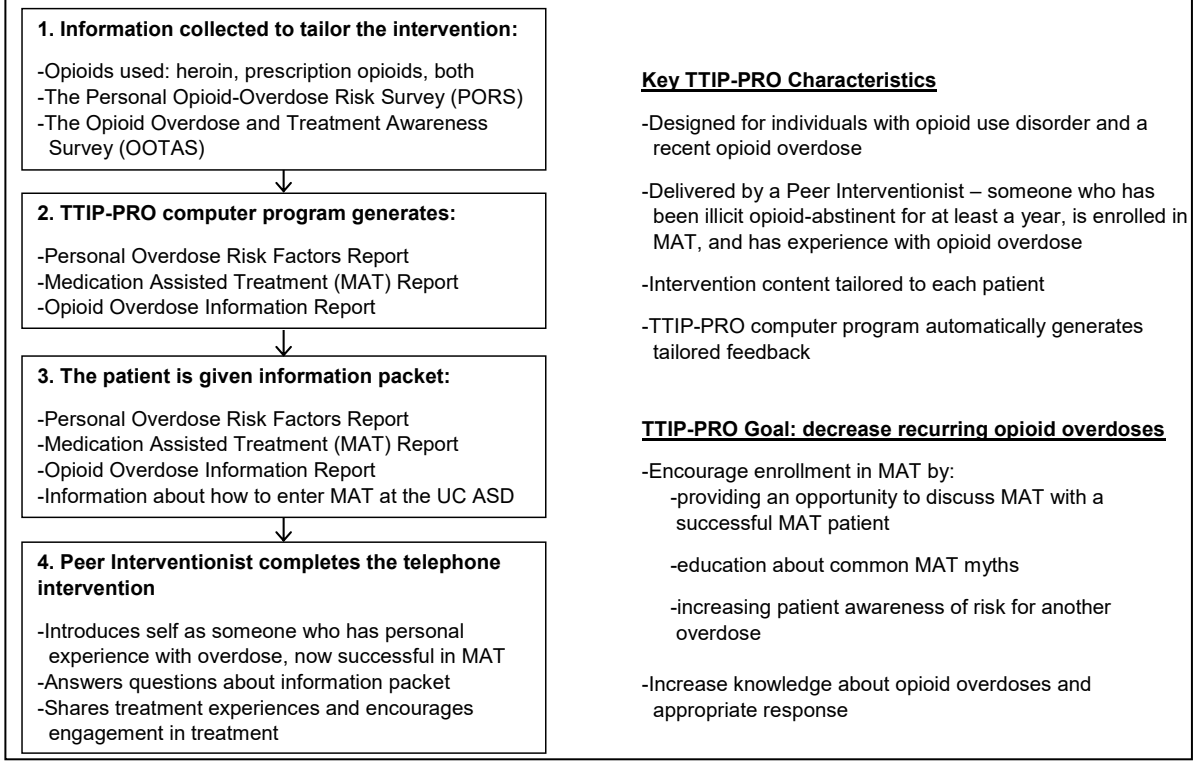
2.1 Control condition

All randomized participants will receive the following information: 1) SAMHSA's "Opioid Overdose Prevention Toolkit: Safety Advice for Patients and Family Members" and "Recovering from Opioid Overdose"; 2) SAMHSA's "Medication-Assisted Treatment for Opioid Addiction: Facts for Families and Friends"; and 3) a list of local methadone and buprenorphine treatment providers. They will also receive a NARCAN® Nasal Spray kit. The NARCAN® Nasal Spray kit is approved by the FDA for reversing OODs and has a favorable side-effects profile.

2.2 TTIP-PRO

An overview of TTIP-PRO, as evaluated in this pilot trial, is provided in **Fig. 2**. A full description of the development and initial testing of TTIP-PRO is described in Winhusen et al.[31] TTIP-PRO consists of two parts: 1) an information packet which includes three reports ("Personal Overdose Risk Factors Report"; "Medication Assisted Treatment (MAT) Report"; and the "Opioid Overdose Information Report") generated from the participant's responses to two surveys and information about how to access treatment at a UC ASD (UC Health/UCPC) MAT program; 2) a 20-minute telephone intervention delivered by Peer Interventionists.

Figure 2. Overview of the Tailored Telephone Intervention Delivered by Peers to Prevent Recurring Opioid-Overdoses



Information Collected to Tailor the Intervention. *The Personal Opioid-Overdose Risk Survey (PORS)*. The PORS assesses an individual's OOD risk factors. It only includes risk factors for which there is documented evidence and scoring for each item was based on the strength of the evidence that the factor increases risk. In order to tailor the questions to reference only the type(s) of opioids used by a given individual, there are three versions of the PORS, one for heroin-only users, one for prescription opioid-only users and one for those who use both heroin and prescription opioids.[31] *The Opioid Overdose and Treatment Awareness Survey (OOTAS).* The OOTAS assesses knowledge about OOD and MAT; like the PORS, there are three versions of the OOTAS to reflect the type(s) of opioids used. The OOTAS is comprised of four sections: 1) OOD risk factors; 2) signs of an OOD; 3) how to respond to an OOD; and 4) myths about MAT. The first 3 sections include only evidence-based items supported by a recent literature review, while items for the 4th section are based on both a literature review and on input from the medical staff of the UC-affiliated methadone program.

The TTIP-PRO Computer Program. The TTIP-PRO data entry and report-generation system has been programmed into REDCap, a software toolset and workflow methodology for collection and management of clinical research data. After an operator enters all relevant information for a particular patient (type of opioid used, responses to the PORS and OOTAS questions), the TTIP-PRO system automatically generates three

reports: 1) "Personal Overdose Risk Factors Report"; 2) "Medication Assisted Treatment (MAT) Report"; and 3) the "Opioid Overdose Information Report." Sample reports for a fictional heroin-only user are provided in **Appendix A**. *The TTIP-PRO Information Packet*. To help prepare the participant for the peer-delivered telephone component, each participant receives a packet with the three reports along with information on how to enroll in treatment at a UC ASD MAT program. *Peer Interventionist Call*. The Peer Interventionists will be provided with a full-set of information related to the three reports so that they can answer participant questions during the call. The primary goal of the call is for the Peer Interventionist to initiate an open exchange of information about MAT (e.g., the Peer Interventionist sharing her/his experiences etc.). The Peer Interventionists are reminded that although the goal is to encourage the participant to enter treatment, it is important to be accepting and supportive if the participant is not currently interested in MAT.

3.0 TTIP-PRO Training, Certification, and Monitoring

3.1 Finalizing Training Materials

A training manual was created and utilized for the TTIP-PRO acceptability study; the Peer Interventionists provided positive feedback about the manual (i.e., provided the essential information succinctly)[31] and, thus, we plan to use a version of this manual updated for the present project (e.g., to reference training tapes and other materials not available in the original project, less focus on the TTIP-PRO generated reports and more on an open exchange of information about MAT). Two important elements missing from the acceptability study, which will be established for the present project, are: 1) training files and 2) an assessment of inter-rater reliability for the competence measure.

3.2 Approach for developing training materials

1. Creating training files. The training files will include 4 mock interventions (1 video, 3 audio) and 4 audio recorded interventions with patient volunteers. The 4 mock interventions will be created by ASD staff members acting as patients/interventionists. The mock interventions will include examples of well-done and poorly-done interventions. Since the intervention is delivered via telephone, the intervention for the training files (with the exception of the video file) will be delivered by phone and will be recorded using a combination of an in-ear microphone and a digital voice recorder. MAT patients meeting criteria to serve as a Peer Interventionist and passing certification will be recruited to create 4 audio training files with patient volunteers. Patient volunteers will be recruited from the UCMC ED and will meet the eligibility criteria outlined above (section 1.3) with the additional requirement of agreeing to have their audio recorded intervention used for training purposes.

2. Inter-rater reliability. Two TTIP-PRO trainers who have been intimately involved with creating TTIP-PRO will rate two training files. Inter-rater reliability will be measured by intraclass correlation coefficients (ICCs).[50, 51] An ICC in the range of .75 - 1.0 reflects excellent agreement.[51] If the ICC is less than .75 then clarifications will be made to the competence assessment and the trainers will rate two additional training files. This process will be repeated until an ICC greater than .75 is achieved. It is anticipated that the 8 training files will be sufficient for establishing reliability but, if needed, additional training files will be created and rated.

3.3 Training and Certification of Peer Interventionists

Potential Peer Interventionists will need to complete training and certification prior to being assigned participants. The process of becoming a certified Peer Interventionist includes the following:

1. Reading the TTIP-PRO Peer Interventionist Manual

2. Attending a training session on the TTIP-PRO Intervention

3. Completing a practice intervention with the assigned trainer.

4. Completing a blank copy of the OOTAS – the trainee needs to get at least 90% of the questions correct to "pass." The OOTAS may be taken more than once.

5. Successfully completing a "mock" intervention. This entails providing the intervention to a person who is not a patient. The trainee's performance will be rated by the trainer using a 3-point scale (1-Meets expectations, 2-Needs improvement, 3-Expectations not met and additional training required). To be certified, the trainee needs to receive a "1" on at least 5 of the 6 abilities assessed:
    1. Ability to provide information while maintaining a conversational tone
    2. Ability to successfully complete the intervention within 20 minutes
    3. Ability to listen
    4. Sufficient familiarity with correct information about OOD and MAT to answer the participant's questions
    5. Ability to remain non-judgmental and encouraging
    6. Ability to avoid confrontation

3.4 Fidelity and Adherence Monitoring

All TTIP-PRO interventions will be audio recorded and rated for adherence/fidelity using the same assessment as that used for certification. Any instance of falling below certification criteria will result in additional training or discontinuation from the trial depending on the nature of the problematic performance.

4.0 Study Procedures

4.1 Schedule of Assessments and Procedures

Table 1 provides an overview of the participant procedures and assessments. Table 2 provides an overview of the assessments that involve the Peer Interventionists.

Table 1. Overview of Study Assessments and Procedures for Study Participants

Assessment/Procedure	Scr/Base/ Random	TTIP-PRO Intervention	3 WK FU call	3 Mo FU visit	6 Mo FU visit	12 Mo FU visit
Completed by	ASD RA	**Peer Interventionist**	ASD RA	ASD RA	ASD RA	ASD RA
Screening Assessments						
Informed consent	X					
Releases of information	X					
Demographics	X					
NIDA modified ASSIST	X					
Efficacy Measures						
MAT Entry Tracking				X	X	X
Opioid Overdose Tracking				X	X	X
Urine drug screen	X			X	X	X
Time line follow-back	X			X	X	X
Safety Measures						
Adverse Events			X	X	X	X
Process Measures						
HOPI			X			
OOTAS	X		X			
Barriers to Treatment	X		X			
Thoughts about abstinence	X		X			
Other Assessments						
Locator Information Form	X			X	X	
PORS	X					X
Utilization of NARCAN®				X	X	X
Interventions						
Provision of OOD and MAT information and NARCAN® Nasal Spray kit (all participants)	X					
TTIP-PRO Intervention		~ 2 weeks post-enroll				
Compensation	$50		$20	$50	$50	$50

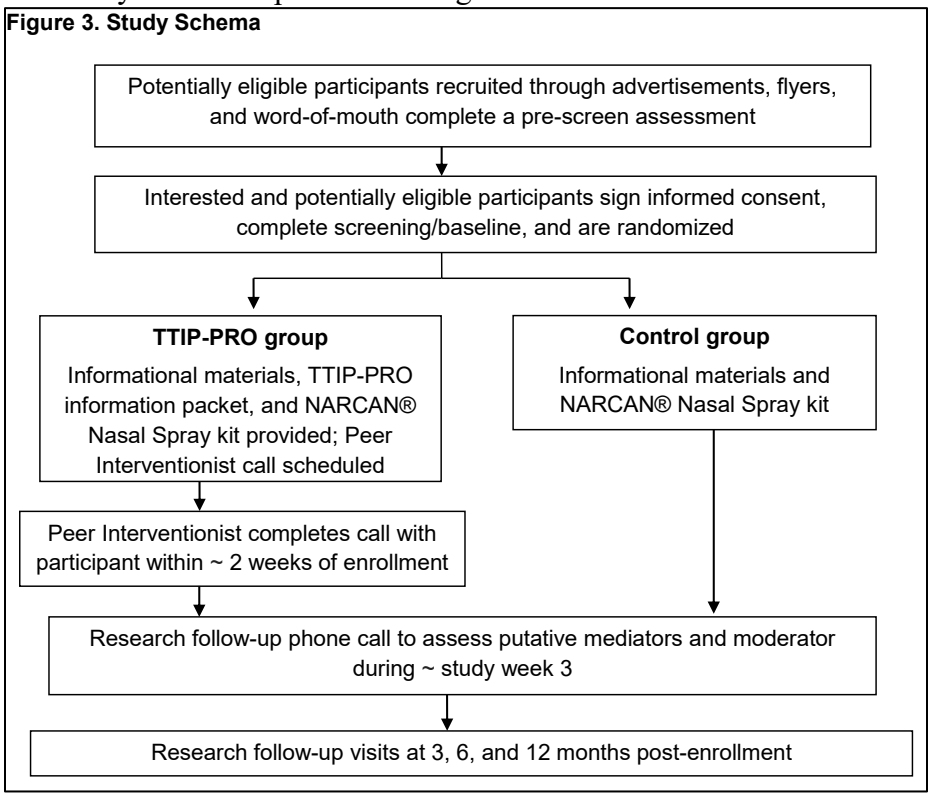
Table 2: Peer Interventionist Assessments

Assessment	Purpose	Collection Schedule
Demographics and eligibility	Document Peer Interventionist study eligibility	Screening/enrollment
The OOTAS –Peer Interventionist Certification	Helps to ensure intervention quality	During certification
Rating of TTIP-PRO sessions	Helps to ensure intervention quality	During certification and throughout the trial
Peer Volunteer Experience Questionnaire (PVEQ)	To obtain feedback on providing TTIP-PRO	End of study participation
PROMIS 10-item measure for Global Health	To assess physical, mental, and social health	Screening/enrollment and every 4 months during participation in pilot trial
Adverse Events	Safety	After every TTIP-PRO session

4.2 Study Schema

The study schema is provided in Figure 3.

Figure 3. Study Schema



4.3 Recruitment and Retention

4.3.1 Recruitment. Potential participants will be recruited through various methods, which include but are not limited to advertisements, flyers, and word-of-mouth. Potential candidates will complete a pre-screen assessment and those who are potentially eligible and interested will be invited to sign informed consent and complete screening/baseline.

4.3.2 Retention. Strategies to maximize retention will include reminder phone calls prior to scheduled appointments and follow-up phone calls and, if needed, certified letters to participants missing a visit. Participants will also be reimbursed up to $220 for their time and travel. Peer Interventionists will be provided with a study cell phone for use in delivering TTIP-PRO and for staying in contact with research staff regarding scheduled and completed interventions. Peer Interventionists will be compensated $40 for completing training/certification, and $20 for each participant for whom they provide the intervention.

5.0 Data Storage and Analysis

5.1 Data Storage and Confidentiality

To maintain participant confidentiality, study records and data will be stored in compliance with the International Conference on Harmonization (ICH) guidelines. Participant records will be held confidential by the use of study codes in the study database, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data. No identifying information will be disclosed in reports, publications or presentations. Information collected for this study will be kept in a locked secure location accessible only to research staff and authorized personnel directly involved with this study.

5.2 Data Analysis

All analyses will be completed on the ITT sample using SAS (SAS Institute, Inc.). Statistical tests will be conducted at a 5% Type I error rate (two-sided) for all measures. It has been recommended that effect sizes be provided rather than using the Bonferroni procedure to adjust for multiple-comparisons; thus, effect sizes and 95% confidence intervals (CI's) will be computed for each treatment effect. For each efficacy analysis, demographic/baseline characteristics and length of time since last OOD will be selected for inclusion in the model using the corrected Akaike Information Criterion (AICC) as the optimizing criterion. For missing data, multiple imputation methods will be used and the resulting model compared to the non-imputed model. **Participant Analyses**-The primary hypothesis, that a significantly greater proportion of TTIP-PRO, relative to control, participants will enter MAT within 12-month follow-up will be tested using a logistic regression (a generalized linear model with a logistic link). Secondary analyses. The key secondary hypothesis, that a significantly lower proportion of TTIP-PRO, relative to control, participants will have a recurring OOD within 12-month follow-up will be tested using a logistic regression (a generalized linear model with a logistic link). The secondary hypothesis that TTIP-PRO, relative to control, participants will have a significantly greater reduction in illicit opioid use will be tested using two outcomes, one based on self-report and the other on UDS results. The proportion of self-reported use days will be treated as a binomial variable and regressed using logistic mixed model regression (random-intercept generalized mixed-model regression with a logistic link function). UDS results (positive for illicit opioids vs. not positive), will be treated as a binary variable which will also be regressed using logistic mixed-model regression. For both outcomes, the effects of interest will be treatment and treatment-by-time interaction.

Power: A pilot study necessitates a limited sample size, and is more useful for showing feasibility than providing an effect size estimate. The proportion of patients who will enroll in a MAT program is unknown for both the TTIP-PRO and control group. Thus, we based the estimated proportions on a recent randomized trial comparing buprenorphine administration during medical hospitalization and linkage to office-based buprenorphine post-discharge to buprenorphine detoxification. In that study, the linkage patients were more likely to enter office-based buprenorphine treatment (72.2%) compared to the detox group (11.9%). The linkage condition was much more intensive than TTIP-PRO and, thus, it is expected that the TTIP-PRO enrollment rate will be considerably less than that observed for the linkage group. Assuming that 12% of our control group enrolls in MAT, and a total sample size of 80, we would have 80% power using a two-tailed test and $\alpha = .05$ to detect a TTIP-PRO effect for a MAT enrollment rate of $\geq 39\%$. In our SBIRT trial, our 12-month follow-up rate was 78%. If 78% of participants complete the 12-month follow-up (n=62) in the proposed trial, we would have 80% power (assuming 12% engagement for the control group, a two-tailed test, and $\alpha = .05$) to detect a TTIP-PRO effect for a MAT enrollment rate of $\geq 46\%$.

Peer Interventionist Analyses - The hypotheses related to the Peer Interventionists will be tested with descriptive statistics. The proportion of Peer Interventionists: 1) attending the training who complete training and certification within the expected 4-hour timeframe and 2) who report being satisfied or very satisfied with their experience as a Peer Interventionist will be calculated.

Analyses for Exploratory Aims- E1 – Testing the validity of the HOPI and PORS. The HOPI was designed to include two subscales (i.e., personally relevant; credible). Factor analyses will be used to determine if the HOPI does, in fact, yield two factors corresponding to the intended subscales. Since the HOPI uses Likert-scale variables, the factor analysis will be based on polychoric correlation. A logistic generalized linear model regression will be used to test the PORS score as a predictor of 1 year OOD rates. The strength of predictive validity will be expressed both as the estimated odds ratio and by area under a ROC curve.

E2 – Testing the conceptual model of TTIP-PRO's mechanisms of change. The purpose of the analyses described here is to explore the degree to which our conceptual model is consistent with the obtained study results. Using all ITT data, we will perform mediation analysis (empirically estimating 95% confidence intervals via bootstrapping) to test three mediation relationships: 1. fear-of-treatment, expected-success, and desire-to-quit as joint mediators of the effect of TTIP-PRO on engagement-in-MAT, 2. desire-to-quit, expected-success, and engagement-in-MAT as joint mediators of the effect of TTIP-PRO on level-of-opioid-use, and 3. knowledge-of-opioid-overdose and level-of-opioid-use as joint mediators of the effect of TTIP-PRO on whether there is an opioid overdose recurrence. We will test whether helpfulness-of-the-intervention (HOPI) respectively moderates the effects of fear-of-treatment, expected-success, desire-to-quit, and knowledge-of-opioid-overdose. We will perform logistic regression when engagement-in-MAT and overdose-recurrence are outcomes and logistic mixed-model regression when opioid use is the outcome.

6.0 Study completion time

An individual participant's period of time for participation and study completion is approximately 12 months. For an individual Peer Interventionist, the time for participation and completion in the pilot trial is approximately 16 months, which includes the time needed for training and certification and for providing TTIP-PRO sessions during the approximately 14-month enrollment period. It is expected that two Peer Interventionists will help to develop the training materials and also participate in the pilot trial; their time of participation and study completion may take up to 24 months. The present project will take less than 3 years to complete.

F. HUMAN SUBJECTS

A detailed data and safety monitoring plan (DSMP), which has been approved by the study sponsor (NIDA) is provided in Appendix B.

Prisoner Status- Due to the illegality of illicit opioid use, many potential participants are likely meet the definition of prisoner (e.g., being in jail or prison, detained in other facilitates as an alternative to criminal prosecution or incarceration, being on probation or parole, being under house arrest or electronic monitoring, etc.). This trial would, thus, be challenging to conduct without allowing the participation of individuals who meet the definition of a prisoner. All randomized participants will receive direct benefit from participating in this trial by receiving: 1) the NARCAN® Nasal Spray kit, which could save their lives if they experience another opioid overdose; 2) information about opioid overdose and substance abuse treatment. For individuals who are, or become during the course of their participation, prisoners, study participation will have no effect on the participant's criminal case, release or parole from jail or prison, or probation case.

G. RISK/BENEFIT ASSESSMENT

This project includes two types of participants: 1) the participants who may receive the TTIP-PRO intervention, referred to as participants, and 2) the participants who will serve as Peer Interventionists.

Risks associated with the TTIP-PRO intervention. TTIP-PRO consists of two parts: 1) an information packet which includes three reports ("Personal Overdose Risk Factors Report"; "Medication Assisted Treatment (MAT) Report"; and the "Opioid Overdose Information Report") generated from the participant's responses to two surveys and information about how to be access treatment at a UC ASD (UC Health/UCPC) MAT program; 2) a 20-minute telephone intervention delivered by Peer Interventionists. The Peer Interventionists interact with the study participants only on the phone, not in person, and, thus, physical safety is not a concern. The phone intervention may last up to 20 minutes during which the Peer Interventionist will answer the participant's questions about the information packet reports, with the potential answers being highly scripted, and an exchange of information between the Peer Interventionist and participant about MAT.

Potential risks of TTIP-PRO for participants include: 1) breach of confidentiality and 2) improper administration of the intervention by the Peer Interventionist. The Peer Interventionists will be provided with the first name and phone number of the participants assigned to them in a secure manner. As part of their training, the Peer Interventionists will be instructed on methods for maintaining confidentiality. Several steps will be taken to ensure proper administration of the intervention. First, all Peer Interventionists must complete a 4-hour training and certification before being assigned study participants as described in section 3.3. Second, all interventions will be audio recorded and rated for adherence/fidelity using the same assessment as that used for certification. Any instance of falling below certification criteria will result in additional training or discontinuation from the trial depending on the nature of the problematic performance.

Potential risks of TTIP-PRO for Peer Interventionists include: 1) breach of confidentiality and 2) increased risk of relapse. In order to diminish the possibility of the participants discovering PHI about the Peer Interventionists, a study cell phone, rather than the Peer Interventionist's personal cell phone will be used; this will avoid the potential for the participant obtaining the Peer Interventionist's phone number and then using the number to determine information about the Peer Interventionist (i.e., name, address). The Peer Interventionists will be exposed to active users during the 20 minute telephone intervention. As noted above, for individuals early in recovery or struggling with recovery and/or other issues, interacting with active users could increase the risk of relapse. Our Peer Interventionist eligibility criteria are designed to select only those individuals whose recovery is sufficiently stable to mitigate this risk. The consent form will clearly delineate relapse as a potential risk. The potential Peer Interventionist will need to agree to an ongoing exchange of information between the research team and his/her treatment providers in order to monitor his/her clinical status. Dr. Winhusen and her research team are co-located with the clinic staff for the UC ASD MAT program and interact on a daily basis; the clinic staff will be instructed to inform the research team of any deterioration in the Peer Interventionist's functioning. In the event of clinical deterioration, the clinic's multi-disciplinary team will develop a treatment plan, which may include the Peer Interventionist's discontinuation from study participation. Peer Interventionists will be compensated $40 for completing training/certification, and $20 for each participant for whom they provide the intervention. Peer Interventionists will not be compensated with cash, which could potentially be used to purchase illicit opioids but, rather, with a prepaid debit card.

Risks associated with study participation. Breach of confidentiality: As with any study, there is a potential risk of loss of confidentiality. To maintain confidentiality, study records and data will be stored in compliance with the International Conference on Harmonization (ICH) guidelines. Participant/Peer Interventionist records will be held confidential by the use of study codes in the study database, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data. No identifying information will be disclosed in reports, publications or presentations. Information collected for this study will be kept in a locked secure location accessible only to research staff and authorized personnel directly involved with this study. Finally, a Certificate of Confidentiality will be obtained for the study. Emotional Discomfort: The participants may experience some

emotional discomfort from answering sensitive and/or personal questions. Participants may experience embarrassment in answering questions about their knowledge of MAT and OOD. The participants/Peer Interventionists can choose to not answer questions that they find to be too uncomfortable and will be reminded that study participation is completely voluntary. NARCAN® Nasal Spray kit. This medication has a very favorable side-effects profile. However, there have been rare cases in which using naloxone to reverse an OOD has resulted in vomiting, sweating, shaking, tachycardia, elevated blood pressure, seizures, pulmonary edema, ventricular dysrhythmias, rapid pulmonary edema, and cardiac arrest.

Benefits. The results of the present pilot study are unlikely to have a direct substantial societal impact. However, promising pilot results would be used in support of a larger trial to test the efficacy of the TTIP-PRO in reducing the recurrence of opioid overdoses. Should that project yield promising results, the benefits to individuals and to society could be substantial. Both the study participants and the Peer Interventionists may directly benefit from study participation in that they will receive information about risks for overdose, the signs of overdose, how to respond to an overdose, and factors that can reduce the risk of an overdose. The study participants may also benefit from receiving a NARCAN® Nasal Spray kit. Consequently, the risk/benefit ratio is favorable and conduct of the research well justified.

H. PAYMENT

Participants will also be reimbursed up to $220 for their time and travel. Peer Interventionists will be provided with a study cell phone for use in delivering TTIP-PRO and for staying in contact with research staff regarding scheduled and completed interventions. Peer Interventionists will be compensated $40 for completing training/certification, and $20 for each participant for whom they provide the intervention. Payments will be provided via a prepaid debit card.

I. SUBJECT COSTS

There are no subject costs for participating in this study.

J. CONSENT FORMS

Attached

K. LITERATURE CITED

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Appendix A: Examples of TTIP-PRO-generated reports for fictional patient

1.0 Example of a "Personal Overdose Risk Factors Report" for a fictional heroin user

Personal Overdose Risk Factors Report

Personal Overdose Risk Factors Report
for Sam
Based on a Survey Taken 02-20-2017

Disclaimer:

You were asked about risk factors that are known to be related to increased risk for having an opioid overdose, but you may have other risk factors that we did not assess. This list of risk factors was generated from the answers that you provided.

Anyone who uses heroin is at risk for an overdose. Based on your answers, there are 11 factors that increase your risk above the risk of just using heroin. These factors include:

Increasing the amount of heroin that you use to get high:
When you use more heroin than you are used to, it becomes much easier to accidentally overdose by using more than your body can handle.

Using heroin by injecting:
Injecting, rather than using by some other method (like smoking or snorting), makes it more likely that you will overdose; the quicker the drug enters your bloodstream, the more likely that the body system that processes the drug will not be able to keep up.

Using benzodiazepines ("benzos" or "nerve pills" like Valium or Xanax) while you are using heroin:
Benzodiazepines can slow down your breathing, just like heroin. If you use them both around the same time, you're much more likely to overdose.

Using alcohol while you are using heroin:
Alcohol can slow down your breathing, just like heroin. If you're drinking around the same time that you're getting high, you're much more likely to overdose.

Using some other drug (like cocaine, ecstasy, marijuana) while you are using heroin:
When you're high on other drugs, your judgment about how much heroin to use may be impaired so even using other drugs that don't slow down breathing may increase your risk of overdose.

Following a period of not using heroin, starting with the amount / dose that you were using prior to being abstinent:
Even one day of not using may lower your tolerance enough so that using your normal amount causes you to overdose.

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Personal Overdose Risk Factors Report

Experiencing depressive symptoms (e.g., feeling sad, lonely, or hopeless):
Depressed opioid users who are not trying to kill themselves are still at higher risk for overdose.

Having decreased liver function, which can be caused by diseases like hepatitis:
When the liver doesn't work as well as it should, it can't process opioids and other drugs as well as it used to. This increases risk of overdose and other medical problems.

Drinking 4 or more alcoholic drinks in a day on a regular basis:
Frequent drinking of alcohol, even if it is not at the same time as using heroin or prescription opioids, has been shown to increase risk of overdose.

Using heroin over a prolonged period. You have been using for 30 years:
Anybody who uses is at some risk for opioid overdose. Long-term users suffer the most overdoses. The longer you've been using, the more likely it is that you'll have an overdose.

Having had an opioid overdose. You have had 30 overdoses:
If you have an overdose and continue using, you're more likely to have another overdose.

Your Personal Risk Survey Score:

The lowest score you can get on the Personal Risk Survey is a 1, with higher scores indicating increasing risk. Based on your answers, your score on the Personal Risk Survey was a 28.

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2.0 Example of a "Medication Assisted Treatment (MAT) Report" for a fictional heroin user

Medication Assisted Treatment (MAT) Report

Medication Assisted Treatment (MAT) Report
for Sam
Based on a Survey Taken 02-20-2017

This report gives you information that you may not know about an effective treatment approach that helps people stop abusing opioids. MAT includes the use of medications like methadone and buprenorphine. (Brand names for buprenorphine include Suboxone® and Zubsolv®.)

Your knowledge of "Medication Assisted Treatment for Opioid Use Disorder" could use a boost. Let's look at the correct answers for the items in that section.

Methadone does not rot your teeth and bones.
A side effect of methadone can be dry mouth, but dental problems arising from dry mouth can be prevented by regular dental hygiene. Some people who are in methadone treatment may complain of an ache in their bones, but this is not a sign of bone rotting. It is a sign of methadone withdrawal -- meaning that their methadone dose may be too low and may need to be adjusted.

Methadone/Suboxone are not worse for your body than heroin/prescription opioids.
Methadone/Suboxone testing, manufacturing, and dispensing all have to follow strict rules to make sure it's safe and effective. On the other hand, drugs purchased on the street are unregulated -- they're often "cut" with other substances, which could lead to overdose and other medical problems.

Methadone and Subutex are safe for a pregnant woman and her unborn child.
Pregnant women treated with Methadone/Subutex have been studied -- the evidence shows that these treatments are safe and effective for this group of people. Being in medication-assisted treatment (instead of continuing illicit opioid use or trying to quit on their own) leads to a better outcome for both the mother and child.

Most people only have to take Methadone/Suboxone once per day to hold off withdrawal and cravings.
Methadone/Suboxone are much longer-acting than heroin and normal prescription opioids. The regular dosing schedule of methadone/Suboxone is once per day, and this usually holds off withdrawal for at least 24 hours.

The statement that people treated with Methadone or Suboxone get high or sleepy and can't safely drive or work is not true.
After reaching a stable dose, people treated with methadone/Suboxone are generally not impaired, and are just as capable as someone who doesn't use.

Page 1

Medication Assisted Treatment (MAT) Report

Methadone and Suboxone do not suppress the immune system.
Studies of people with impaired immune systems (from HIV) have found better outcomes for former drug users being treated with methadone, compared to drug users who continued using street drugs.

The statement that lower doses of Methadone/Suboxone are always better than higher doses is not true.
Each individual has unique needs, and a doctor will help find the right dose for the person -- a low dose may work very well for one person, but their friend may need twice the dose. What's important is that the person is on a dose that is high enough to hold off withdrawal and cravings.

Methadone and Suboxone are effective treatments, not just substitutes for heroin and prescription opioids.
Using methadone/suboxone as prescribed does not give the high that people get from using heroin/prescription opioids -- but it is a safe, proven way to prevent withdrawal and to let the individual lead a healthier, happier life.

3.0 Example of an "Opioid Overdose Information Report" for a fictional heroin user

Opioid Overdose Information Report

Opioid Overdose Information Report
for Sam
Based on a Survey Taken 02-20-2017

It may help you in the future to have a good working knowledge of the risks for overdose, the signs of overdose, and how to respond to an overdose.

Risks for Opioid Overdose

Your knowledge of "Risks for Opioid Overdose" could use a boost. Let's look at the correct answers for the items in that section."

Using heroin after a period of non-use (for example after release from prison/jail or discharge from detox treatment) is a risk factor for opioid overdose.
Even one day of not using may lower your tolerance enough so that using your normal amount causes you to overdose.

Using heroin with other substances like alcohol or benzodiazepines ("benzos" or "nerve pills" such as Xanax or Valium) is a risk factor for opioid overdose.
Opioids suppress your ability to breathe normally; using other drugs that slow down breathing, like alcohol or benzodiazepines, increases your chances of overdose.

A short history (less than 1 year) of using heroin does not increase the risk of overdose.
Most first-time overdoses happen after using for at least a year -- a longer history of using opioids is associated with more risk of having an overdose.

Having decreased liver function, which can result from certain diseases like hepatitis, does increase the risk of overdose.
The liver processes opioids so they can leave the body -- hepatitis and other diseases that decrease liver function can affect this processing, and increase the risk of overdosing.

Having prior opioid overdoses is a risk factor for having an overdose.
Those who have overdosed in the past are likely to overdose again as they continue using.

Page 1

Opioid Overdose Information Report

Using heroin by smoking, snorting, or taking pills rather than by injecting (needle and syringe) does not increase the risk of overdose. Injecting is riskier.
Injecting gets the drug into your body much quicker than any other way of using -- the quicker rate of entry leads to a greater risk of absorbing too much of the drug at one time and overdosing.

Using heroin that is more pure than usual does increase the risk of overdose.
Putting more of the drug into your body than it is used to makes it more likely that your breathing will slow down or stop.

Being enrolled in methadone- or Suboxone-maintenance treatment actually decreases the risk of overdose.
Being in medication-assisted treatment means that the person is being medically treated for addiction in a way that is proven to be safe and effective.

Having depressive symptoms (e.g., feeling sad, lonely, or hopeless) does increase the risk of overdose.
Even when they do not intend to harm themselves or commit suicide, users who have symptoms of depression are more likely to overdose.

Drinking alcohol almost every day does increase the risk of opioid overdose.
Drinking alcohol more frequently is associated with greater risk for overdose

Signs of Opioid Overdose

Your knowledge of "Signs of Opioid Overdose" could use a boost. Let's look at the correct answers for the items in that section.

Blue skin is a sign of an opioid overdose.
Blue skin means that the person is not getting enough oxygen and needs immediate medical help.

The body being very limp is a sign of an opioid overdose.
In an overdose, the muscles may go very limp, and the person will not be able to move.

Bloodshot eyes are not a sign of an opioid overdose.
Bloodshot eyes aren't typical of opioid overdoses -- however, the pupils (black part of the eyes) may be very small.

Page 2

Opioid Overdose Information Report

The face being very pale or clammy is a sign of an opioid overdose.
Lack of blood flow and oxygen cools the skin and takes the color from the skin.

Slow pulse, irregular pulse, or no pulse is a sign of an opioid overdose.
In an overdose, the heart usually slows down and may eventually stop beating if medical treatment isn't given.

Throwing up is a sign of an opioid overdose.
Even though throwing up is a common side effect of getting high on opioids, a person who has overdosed may be throwing up a lot more than usual -- if they choke on their vomit, then they may die.

Acting upset and irritated is not a sign of an opioid overdose.
Someone who has overdosed on opioids will usually appear to be in a very deep sleep, with slow breathing.

Passing out is a sign of an opioid overdose.
It may be hard to tell the difference between someone being really high and passed out -- if they don't respond to loud noises, and their breathing is very slow or stopped, then they probably have passed out, and you should call for medical help.

Choking sounds or a gurgling/snoring noise is a sign of an opioid overdose.
These are signs that the person is not breathing normally, and may be close to death.

Slow breathing, irregular breathing, or not breathing is a sign of an opioid overdose.
The main problem of opioid overdose is that breathing slows down and eventually stops.

Acting really paranoid is not a sign of an opioid overdose.
Someone who has overdosed on opioids will probably not be acting paranoid -- they will probably be passed out.

Not responding to yelling or pinching or other intense stimulation is a sign of an opioid overdose.
Non-responsiveness is a sign that the person has lost consciousness.

Page 3

Opioid Overdose Information Report

Responses to Opioid Overdose

Your knowledge of "Responses to Opioid Overdose" could use a boost. Let's look at the correct answers for the items in that section.

911 should be called if someone has overdosed. The quicker 911 is called the more likely the person is to be saved.
An overdose is a life-threatening medical emergency that needs immediate attention - you don't have to tell the dispatcher that drugs are involved - just that someone is not breathing and is unresponsive.

Putting the person in a bathtub full of cold water does not stop or slow down an overdose.
This will not bring the person out of an overdose, and instead it might cause other problems, like shock or hypothermia.

Laying the person on their back is not helpful.
A person who has overdosed should be placed on their side, with their airway cleared, to prevent them from choking on their own vomit.

Giving the person mouth-to-mouth breathing may help save their life.
When death occurs from overdose, it is almost always because the person stopped breathing - while you're waiting for medical help to arrive, you can breathe for them.

Giving the person naloxone (Narcan), if you have it, is a potentially life-saving thing to do.
Naloxone (Narcan) is the ONLY chemical that can reverse an opioid overdose - other things like cocaine, coffee, or salt water will not help and probably make things worse.

Walking the person around is not helpful.
Walking the person around wastes time and may even speed up the overdose.

Injecting the person with cocaine or methamphetamine may make the overdose worse.
Breathing slows down during an overdose which reduces the amount of oxygen in the body. Injecting cocaine and/or methamphetamine increases heart rate, causing the body to need more oxygen.

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Appendix B: Data Safety and Monitoring Plan (DSMP)

Data and Safety Monitoring Plan

1 R34 DA040862-01

A Tailored, Peer-delivered Intervention to Reduce Recurring Opioid Overdoses

PI: Theresa Winhusen, PhD, University of Cincinnati

Medical Monitor: Michael Lyons, MD, University of Cincinnati

October 27, 2017

I. SUMMARY OF PROTOCOL

1. Brief description of the protocol: This project will further develop and test the Tailored Telephone Intervention delivered by Peers to Prevent Recurring Opioid Overdoses (TTIP-PRO), an intervention to facilitate entry into medication assisted treatment (MAT) for individuals experiencing a non-fatal opioid overdose (OOD). Specific aims are to: 1) Finalize the Peer Interventionist training materials (Stage IA); and 2) Conduct pilot testing in preparation for a full-scale clinical trial (Stage IB). Approximately 80 adults, who have been treated for an OOD within the past 6 months, will be randomized into the pilot study. Participants randomized to the control condition will receive contact information about local MAT programs, SAMHSA information about OOD and about MAT, and a NARCAN® Nasal Spray kit; all of which will be provided during the enrollment visit. Participants randomized to the experimental condition will receive TTIP-PRO in addition to the elements provided in the control condition. TTIP-PRO consists of two parts: 1) an information packet which includes three reports ("Personal Overdose Risk Factors Report"; "Medication Assisted Treatment (MAT) Report"; and the "Opioid Overdose Information Report") generated from the participant's responses to two surveys and information about how to access treatment at a UC ASD (UC Health/UCPC) MAT program; 2) a 20-minute telephone intervention delivered by Peer Interventionists. The TTIP-PRO intervention will be provided within 2 weeks of the enrollment visit. All participants will complete a follow-up phone call in week 3 and in-person visits at 3, 6-, and 12-months following enrollment. Exploratory analyses will test our conceptual model of TTIP-PRO's mechanisms of change and the validity of two assessments developed for TTIP-PRO.

2. Primary and secondary outcome measures: Enrollment in MAT (Yes/No) within the 12-month follow-up period is the primary outcome measure. Secondary outcomes include experiencing an OOD (Yes/No) within the 12-month follow-up and change in opioid use, as measured by the Timeline Follow-back (TLFB) procedure and urine drug screens (UDS), between baseline and 12-month follow-up. Process measures include: Barriers to Treatment Inventory- the Fear of Treatment subscale will be evaluated as a mediator of TTIP-PRO's efficacy. Thoughts about abstinence will assess desire to quit illicit opioid use and expected success in quitting, which will be evaluated as mediators. The Opioid Overdose and Treatment Awareness Survey (OOTAS) assesses knowledge about OOD and MAT; the total OOTAS score will be evaluated as a mediator of TTIP-PRO's efficacy. The Helpfulness of Peer Intervention (HOPI) will assess the degree to which participants perceived TTIP-PRO to be personally relevant and credible; the total score will be tested as a moderator. Peer Interventionist Measures include: 1) the Peer Volunteer Experience Questionnaire (PVEQ) will be used to obtain feedback from peer volunteers delivering TTIP-PRO; and 2) the PROMIS 10-item measure for Global Health.

3. Inclusion/exclusion criteria:

This project includes two types of participants: 1) the participants who may receive the TTIP-PRO intervention, referred to as participants, and 2) the participants who will serve as Peer Interventionists.

Participants

All potential participants will be recruited through various methods, which include but are not limited to advertisements, flyers, and word-of-mouth. Eligible participants will meet all inclusion, and no exclusion criteria:

Inclusion Criteria:

1) Report having been treated for an OOD within the past 6 months;

2) Age 18 years or older;

3) Scores "high risk" for heroin and/or non-medical use of prescription opioids on the NIDA

modified ASSIST (i.e., ≥ 27);

4) Be able to understand the study, and having understood, provide written informed consent in English;

5) Access to a phone (for TTIP-PRO intervention and phone follow-up);

6) Be willing to have their intervention audio recorded and rated if randomized to TTIP-PRO;

7) Have an opioid-positive baseline/screening urine drug screen.

Exclusion Criteria*:*

1) In the judgment of the investigator, would not be expected to complete the study protocol (e.g., due to relocation from the clinic area, probable incarceration, etc.);

2) Current engagement in addiction treatment;

3) Residence more than 40 miles from the location of follow-up visits;

4) Inability to provide sufficient contact information (must provide at least 2 reliable locators);

5) Prior participation in the current study.

Peer Interventionists

All potential Peer Interventionists will be recruited primarily by word of mouth from a UC Addiction Sciences Division (ASD) Medication Assisted Treatment (MAT) clinic (i.e., methadone or buprenorphine). For individuals early in recovery or struggling with recovery and/or other issues, interacting with active users could increase their risk of relapse. Our Peer Interventionist eligibility criteria are designed to select only those whose recovery is sufficiently stable to mitigate this risk.

Inclusion Criteria:

1) Age 18 years or older;

2) Enrolled in UC ASD (i.e., UC Health/UCPC) MAT program;

3) Enrolled in a MAT program for at least one year;

4) Report being abstinent from illicit opioids for at least one year;

5) Report having experienced, witnessed, and/or lost a family member or friend to an overdose.

Exclusion Criteria:

1) Unwilling to sign a release of information (ROI) to allow research staff to confirm pertinent eligibility criteria and to monitor clinical status with UC ASD (i.e., UC Health/UCPC) MAT clinical staff;
2) Clinical staff from their program have significant concerns about their participation;
3) Unwilling to have their sessions audio recorded and assessed by a TTIP-PRO trainer.

4) Specific plan to leave the UC ASD (i.e., UC Health/UCPC) MAT program within the next 6 months

4. Sample size: Participants: Approximately 38 participants will be recruited to develop training audio files (Aim 1) Approximately 80 participants will be randomized into the pilot efficacy trial.

   Peer Interventionists: Approximately 15 Peer Interventionists will participate.

II. TRIAL MANAGEMENT

1. List of participating enrolling clinics or data collection centers: All participants will be recruited by the University of Cincinnati Addiction Sciences Division (ASD). This is a single site study; all data will be collected at the University of Cincinnati.

2. Projected timetable: This is a three-year study. Finalizing the Peer Interventionist training materials (Aim 1) will be accomplished within Year 1 as will the pre-initiation tasks for the pilot clinical trial. Conducting the trial, completing data analyses, and writing the final report will be accomplished during years 1.5 – 3.

3. Target population distribution: Our planned enrollment is based on the demographics of the populations from which we will be recruiting. Of the 102 participants, we anticipate enrolling 34 (33%) females and 68 (67%) males, 9 (9%) black or African American, 1 (1%) American Indian/Alaska Native, and 92 (90%) white participants. Additionally, we will enroll 1 (1%) Latino or Hispanic and 101 (99%) not Latino or Hispanic. Of the 15 Peer Interventionists, we anticipate enrolling 14 (93%) females and 1 (7%) males, 1 (7%) black or African American, and 14 (93%) white. Additionally, we will enroll 15 (100%) not Latino or Hispanic.

III. DATA MANAGEMENT AND ANALYSIS

1. Data acquisition and transmission: All data will be acquired from participant interviews, clinic records, or urine drug screens. All research staff will be trained in Good Clinical Practice (GCP) guidelines. All data will be de-identified. Only research staff members directly involved with the study will have access to identifying information for the participants and Peer Interventionists. TTIP-PRO interventions will be audio recorded using a combination of an in-ear microphone and a digital voice recorder for fidelity monitoring. Recordings will be provided as MP3 or other digital format sound files to the TTIP-PRO trainers in person or via a secure electronic data repository provided by UC ("Box at UC") which has an encrypted area for this purpose.

2. Data entry methods: All de-identified demographic and clinical data will be managed in REDCap, a software toolset and workflow methodology for collection and management of clinical research data developed by Vanderbilt University, in collaboration with institutional partners including the University of Cincinnati Academic Health Center. Only the necessary study personnel will have access to the database. Case report forms (CRFs) that are more complex, including Timeline Follow-back (TLFB) and tracking of treatment and OOD, which will entail transcription from medical records, will first be completed on paper and then entered into the electronic database. All other CRFs will be direct data entry, with paper versions used only if there are technical issues with the database. Any data entered from a paper CRF will be double entered by two separate research staff members and compared to ensure the integrity of the information.

3. Data analysis plan: All analyses will be completed on the ITT sample using SAS, Version 9.4 (SAS Institute, Inc.). Statistical tests will be conducted at a 5% Type I error rate (two-sided) for all measures. It has been recommended that effect sizes be provided rather than using the Bonferroni procedure to adjust for multiple-comparisons; thus, effect sizes and 95% confidence intervals (CI's) will be computed for each treatment effect. For each efficacy analysis, demographic/baseline characteristics and length of time since last OOD will be selected for inclusion in the model using the corrected Akaike Information Criterion (AICC) as the optimizing criterion. For missing data, multiple imputation methods will be used and the resulting model compared to the non-imputed model.

Participant Analyses-The primary hypothesis, that a significantly greater proportion of TTIP-PRO, relative to control, participants will enter MAT within 12-month follow-up will be tested using a logistic regression (a generalized linear model with a logistic link). Secondary analyses. The key secondary hypothesis, that a significantly lower proportion of TTIP-PRO, relative to control, participants will have a recurring OOD within 12-month follow-up will be tested using a logistic regression (a generalized linear model with a logistic link). The secondary hypothesis that TTIP-PRO, relative to control, participants will have a significantly greater

reduction in illicit opioid use will be tested using two outcomes, one based on self-report and the other on UDS results. The proportion of self-reported use days will be treated as a binomial variable and regressed using logistic mixed model regression (random-intercept generalized mixed-model regression with a logistic link function). UDS results (positive for illicit opioids vs. not positive), will be treated as a binary variable which will also be regressed using logistic mixed-model regression. For both outcomes, the effects of interest will be treatment and treatment-by-time interaction.

Power: A pilot study necessitates a limited sample size, and is more useful for showing feasibility than providing an effect size estimate. The proportion of patients who will enroll in a MAT program is unknown for both the TTIP-PRO and control group. Thus, we based the estimated proportions on a recent randomized trial comparing buprenorphine administration during medical hospitalization and linkage to office-based buprenorphine post-discharge to buprenorphine detoxification. In that study, the linkage patients were more likely to enter office-based buprenorphine treatment (72.2%) compared to the detox group (11.9%). The linkage condition was much more intensive than TTIP-PRO and, thus, it is expected that the TTIP-PRO enrollment rate will be considerably less than that observed for the linkage group. Assuming that 12% of our information-only control group enrolls in MAT, and a total sample size of 80, we would have 80% power using a two-tailed test and $\alpha = .05$ to detect a TTIP-PRO effect for a MAT enrollment rate of $\geq 39\%$. In our SBIRT trial, our 12 month follow-up rate was 78%. If 78% of participants complete the 12 month follow-up (n=62) in the proposed trial, we would have 80% power (assuming 12% engagement for the control group, a two-tailed test, and $\alpha = .05$) to detect a TTIP-PRO effect for a MAT enrollment rate of $\geq 46\%$.

Peer Interventionist Analyses - The hypotheses related to the Peer Interventionists will be tested with descriptive statistics. The proportion of Peer Interventionists: 1) attending the training who complete training and certification within the expected 4-hour timeframe and 2) who report being satisfied or very satisfied with their experience as a Peer Interventionist will be calculated.

Analyses for Exploratory Aims- E1 – Testing the validity of the HOPI and PORS. The HOPI was designed to include two subscales (i.e., personally relevant; credible). Factor analyses will be used to determine if the HOPI does, in fact, yield two factors corresponding to the intended subscales. Since the HOPI uses Likert-scale variables, the factor analysis will be based on polychoric correlation. A logistic generalized linear model regression will be used to test the PORS score as a predictor of 1 year OOD rates. The strength of predictive validity will be expressed both as the estimated odds ratio and by area under a ROC curve.

E2 – Testing the conceptual model of TTIP-PRO's mechanisms of change. The purpose of the analyses described here is to explore the degree to which our conceptual model is consistent with the obtained study results. Using all ITT data, we will perform mediation analysis (empirically estimating 95% confidence intervals via bootstrapping) to test three mediation relationships: 1. fear-of-treatment, expected-success, and desire-to-quit as joint mediators of the effect of TTIP-PRO on engagement-in-MAT, 2. desire-to-quit, expected-success, and engagement-in-MAT as joint mediators of the effect of TTIP-PRO on level-of-opioid-use, and 3. knowledge-of-opioid-overdose and level-of-opioid-use as joint mediators of the effect of TTIP-PRO on whether there is an opioid overdose recurrence. We will use the data from participants receiving TTIP-PRO to test whether helpfulness-of-the-intervention (HOPI) respectively moderates the effects of fear-of-treatment, expected-success, desire-to-quit, and knowledge-of-opioid-overdose. We will perform logistic regression when engagement-in-MAT and overdose-recurrence are outcomes and logistic mixed-model regression when opioid use is the outcome.

IV. QUALITY ASSURANCE

1. Procedures in place to ensure the validity and integrity of the data: A modified version of a training manual developed for an earlier acceptability study of TTIP-PRO will be utilized. Two important elements missing from the acceptability study, which will be established for the present project, are: 1) training files and 2) an assessment of inter-rater reliability for the competence measure. The training files will include 4 mock interventions (1 video, 3 audio) and 4 audio recorded interventions with patient volunteers. Two TTIP-PRO trainers will rate two training files. Inter-rater reliability will be measured by intraclass correlation coefficients

(ICCs). If the ICC is less than .75 then clarifications will be made to the competence assessment and the trainers will rate two additional training files. This process will be repeated until an ICC greater than .75 is achieved. All TTIP-PRO sessions will be rated for providing fidelity and adherence by one of the two TTIP-PRO trainers. Potential Peer Interventionists will need to complete training and certification prior to being assigned participants.

2. Procedures to guarantee the accuracy and completeness of the data during data collection, entry, transmission and analysis: Assessments programmed in REDCap will use validation rules, integrity checks, and hard stops as needed to ensure that data are as complete and accurate as possible. The RA will check any data collected by paper source for completeness. As previously described, all data entered from a paper source will be double-entered and checked for consistency by REDCap.

V. REGULATORY ISSUES

1. Reporting of AEs/ SAEs to the IRB, NIDA, and the FDA: All SAEs will be reported to the IRB and NIDA within 72 hours of their discovery. This is a behavioral study and so FDA reporting is not required. We will use FDA criteria for SAEs (i.e., an adverse event that results in any of the following outcomes; death, life threatening, requires hospitalization, initial or prolonged, results in disability, congenital anomaly, requires intervention to prevent permanent impairment or damage, or other significant medical event); OOD will be treated as an SAE. Dr. Lyons or the designated study physician will assess the severity, relatedness, and outcome of each AE and SAE. It will also be Drs. Lyons', Winhusen's, and Wilder's responsibility to manage all AEs and SAEs and to make referrals for appropriate care, as necessary. All participant information will be de-identified when reporting SAEs. All AEs and SAEs will be reported to and reviewed by the DSMB at the time of their standard meeting, except when Dr. Lyons or the designated study physician thinks that the SAE is very severe and/or may require a protocol amendment. In that case, Dr. Winhusen may request an ad hoc review by the DSMB. All AEs and SAEs will be entered into a database that is de-identified and password protected to ensure confidentiality.

2. Reporting of IRB action to NIDA: All communications with and actions of the IRB will be kept in a regulatory binder specific for this study. Any protocol changes, amendments, or deviations will be submitted to the IRB and NIDA and the IRB's actions will then be reported to NIDA. Any other IRB actions (including annual re-approvals and correspondence related to DSMB reports) will be submitted to NIDA.

3. Report of changes or amendments to the protocol: All changes and amendments to the protocol will be submitted to the IRB and NIDA. Only after IRB and NIDA approvals are granted will the changes and amendments be implemented.

4. Trial stopping rules: Individual study participants will be informed of their right to discontinue study participation at any time during the study. The PI/Medical Monitor may discontinue a participant or Peer Interventionist's trial participation if deemed clinically appropriate. The DSMB may recommend study termination based on review of site performance or safety and efficacy data. NIDA has the right to discontinue the investigation at any time.

5. Disclosure of conflict of interest: The investigators and members of the data safety and monitoring board (DSMB) have no conflicts of interest.

VI. TRIAL SAFETY

1. Potential risks and benefits for participants: This project includes two types of participants: 1) the participants who may receive the TTIP-PRO intervention, referred to as participants, and 2) the participants who will serve as Peer Interventionists.

Risks associated with the TTIP-PRO intervention. TTIP-PRO consists of two parts: 1) an information packet which includes three reports ("Personal Overdose Risk Factors Report"; "Medication Assisted Treatment (MAT) Report"; and the "Opioid Overdose Information Report") generated from the participant's responses to two surveys and information about how to be access treatment at a UC ASD (UC Health/UCPC) MAT program; 2) a 20-minute telephone intervention delivered by Peer Interventionists. The Peer Interventionists interact with the study participants only on the phone, not in person, and, thus, physical safety is not a concern. The phone intervention may last up to 20 minutes during which the Peer Interventionist will answer the participant's questions about the information packet reports, with the potential answers being highly scripted, and an exchange of information between the Peer Interventionist and participant about MAT.

Potential risks of TTIP-PRO for participants include: 1) breach of confidentiality and 2) improper administration of the intervention by the Peer Interventionist. The Peer Interventionists will be provided with the first name and phone number of the participants assigned to them in a secure manner. As part of their training, the Peer Interventionists will be instructed on methods for maintaining confidentiality. Several steps will be taken to ensure proper administration of the intervention. First, all Peer Interventionists must complete a 4-hour training and certification before being assigned study participants. For certification, a TTIP-PRO trainer will rate the trainee's performance on a mock intervention. The trainer will use a 3-point scale (1-Meets expectations, 2-Needs improvement, 3-Expectations not met and additional training required). To be certified, the trainee needs to receive a "1" on at least 5 of the 6 abilities assessed: 1) Ability to provide information while maintaining a conversational tone; 2) Ability to successfully complete the intervention within 20 minutes; 3) Ability to listen; 4) Sufficient familiarity with correct information about OOD and MAT to answer the participant's questions; 5) Ability to remain non-judgmental and encouraging; and 6) Ability to avoid confrontation. Second, all interventions will be audio recorded and rated for adherence/fidelity using the same assessment as that used for certification. Any instance of falling below certification criteria will result in additional training or discontinuation from the trial depending on the nature of the problematic performance.

Potential risks of TTIP-PRO for Peer Interventionists include: 1) breach of confidentiality and 2) increased risk of relapse. In order to diminish the possibility of the participants discovering PHI about the Peer Interventionists, a study cell phone, rather than the Peer Interventionist's personal cell phone will be used; this will avoid the potential for the participant obtaining the Peer Interventionist's phone number and then using the number to determine information about the Peer Interventionist (i.e., name, address). The Peer Interventionists will be exposed to active users during the 20 minute telephone intervention. As noted above, for individuals early in recovery or struggling with recovery and/or other issues, interacting with active users could increase the risk of relapse. Our Peer Interventionist eligibility criteria are designed to select only those individuals whose recovery is sufficiently stable to mitigate this risk. The consent form will clearly delineate relapse as a potential risk. The potential Peer Interventionist will need to agree to an ongoing exchange of information between the research team and his/her treatment providers in order to monitor his/her clinical status. Dr. Winhusen and her research team are co-located with the clinic staff for the UC ASD MAT program and interact on a daily basis; the clinic staff will be instructed to inform the research team of any deterioration in the Peer Interventionist's functioning. In the event of clinical deterioration, the clinic's multi-disciplinary team will develop a treatment plan, which may include the Peer Interventionist's discontinuation from study participation. Peer Interventionists will be compensated $40 for completing training/certification, and $20 for each participant for whom they provide the intervention. Peer Interventionists will not be compensated with cash, which could potentially be used to purchase illicit opioids but, rather, with a prepaid debit card.

Risks associated with study participation. Breach of confidentiality: As with any study, there is a potential risk of loss of confidentiality. To maintain confidentiality, study records and data will be stored in compliance with the International Conference on Harmonization (ICH) guidelines. Participant/Peer Interventionist records will be held confidential by the use of study codes in the study database, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data. No

identifying information will be disclosed in reports, publications or presentations. Information collected for this study will be kept in a locked secure location accessible only to research staff and authorized personnel directly involved with this study. Finally, a Certificate of Confidentiality will be obtained for the study. Emotional Discomfort: The participants may experience some emotional discomfort from answering sensitive and/or personal questions. Participants may experience embarrassment in answering questions about their knowledge of MAT and OOD. The participants/Peer Interventionists can choose to not answer questions that they find to be too uncomfortable and will be reminded that study participation is completely voluntary. NARCAN® Nasal Spray kit. This medication has a very favorable side-effects profile. However, there have been rare cases in which using naloxone to reverse an OOD has resulted in vomiting, sweating, shaking, tachycardia, elevated blood pressure, seizures, pulmonary edema, ventricular dysrhythmias, rapid pulmonary edema, and cardiac arrest.

Benefits. The results of the present pilot study are unlikely to have a direct substantial societal impact. However, promising pilot results would be used in support of a larger trial to test the efficacy of the TTIP-PRO in reducing the recurrence of opioid overdoses. Should that project yield promising results, the benefits to individuals and to society could be substantial. Both the study participants and the Peer Interventionists may directly benefit from study participation in that they will receive information about risks for overdose, the signs of overdose, how to respond to an overdose, and factors that can reduce the risk of an overdose. The study participants may also benefit from receiving a NARCAN® Nasal Spray kit. Consequently, the risk/benefit ratio is favorable and conduct of the research well justified.

2. Collection and reporting of AEs and SAEs: In general, the risks associated with trials employing behavioral interventions are presumed minimal relative to those evaluating pharmacologic interventions. Based on the TTIP-PRO acceptability study the risk from TTIP-PRO is low. Still, for the present trial, the population studied is a vulnerable population and possibly at higher risk given the nature of the disorder and the population. Thus, the following events, which are not defined as SAEs, will be tracked on an AE CRF for participants and Peer Interventionists:

1. Suicidal ideation
2. Homicidal ideation

In addition, the following events will be track on an AE CRF for the Peer Interventionists:

1. Discharge from MAT program for any reason
2. Illicit opioid use
3. Other clinical deterioration as reported by clinic staff

For TTIP-PRO, which is a behavioral trial, the RA is primarily responsible for assessing the occurrence of AEs/SAEs with oversight by the Study Medical Monitor and PI. For Participants, the RA will query about how s/he has been feeling since the last visit (i.e., at the follow-up phone call in week 3 and in-person visits at 3, 6-, and 12-months following enrollment). For Peer Interventionists, the RA will query about how s/he has been feeling following the delivery of each TTIP-PRO intervention. All AEs/SAEs occurring during the course of the clinical trial will be collected, documented, and reported by the investigator or sub-investigators in accordance with reporting requirements. Dr. Lyons or the designated study physician will assess the severity, causality and outcome of all AEs and SAEs. It will also be Drs. Lyons', Winhusen's, and Wilder's responsibility to manage all AEs and SAEs and to make referrals for appropriate care, as necessary. All SAEs will be reported to the University of Cincinnati Institutional Review Board and the NIDA project officer within 72 hours of their discovery. All subject information will be de-identified when reporting serious adverse events.

3. Management of SAEs or other study risks: Please refer to Section VI. 1. for management of study risks.

VII. TRIAL EFFICACY

1. Plans for interim analysis of efficacy data: There will be no interim analysis of efficacy data by the investigators. However, the DSMB (see below, Section IX, 5) will monitor efficacy data and provide recommendations regarding whether the study should continue without modification or with modification or be terminated.

VIII. DSM PLAN ADMINISTRATION

1. Responsibility for data and safety monitoring: Drs. Winhusen, Lyons, and Wilder will be responsible for the clinical management and safety monitoring of the study participants and Peer Interventionists.

2. Frequency of DSM reviews: The study protocol will be reviewed by the DSMB before recruitment starts. Efficacy and AE/SAE data will be reviewed by the DSMB every six months for the duration of the trial. The DSMB reports will be submitted to the IRB and NIDA. Additionally, annual reports will be sent to the IRB for re-approval of the study. SAEs will be reported and reviewed by the DSMB at the time of their meeting, except when Dr. Lyons or the designated study physician thinks that the SAE is very severe and/or may require a protocol amendment. In that case, Dr. Winhusen may request an ad hoc review by the DSMB. Each SAE will be reported in writing at the time of occurrence (within 72 hours) to the IRB and NIDA.

3. Content of DSM report: The DSM report will include a brief description of the trial and any changes made to the trial. Additionally, we will report baseline sociodemographic characteristics, including age, gender, and race of the subjects screened and randomized. We will also report retention rates and the disposition for all study participants and Peer Interventionists. Finally, any quality assurance issues, regulatory issues, AEs and SAEs will be included in the report. After review of the data, the DSM report will make recommendations about whether the trial should continue with or without modifications or be terminated.

IX. DSM BOARD (DSMB) PLAN

1. Members and affiliation: Members for the DSMB will include: 1. Marepalli Rao, PhD, Professor, University of Cincinnati College of Medicine, who has extensive expertise in data analysis for clinical trials. 2. Shawn Ryan, MD, MBA who is an emergency medicine physician at the University of Cincinnati Medical Center. 3. Darcelia Plott, MD, staff Psychiatrist at the Cincinnati Veterans Medical Center, who is board certified in both Internal Medicine and Addiction Medicine.

2. Frequency of meetings: The DSMB will meet before recruitment starts, and then every six months. The PI may request an ad hoc review more frequently if protocol amendments are needed.

3. Conflict of interest: The DSMB members report no conflicts.

4. Protection of confidentiality: All participant data will be de-identified prior to review by the DSMB to maintain participant confidentiality. Only participant ID number, gender, age, and race will be provided to the DSMB.

5. Monitoring activities (initial and ongoing study review): The DSMB will review the protocol prior to participant enrollment and will provide recommendations for any protocol changes in order to maximize safety or efficacy assessments. The DSMB will then formally meet before recruitment starts, then at a minimum of every 6 months during the course of the study. The DSMB will review the disposition of all study participants and reasons for study drop-out. The DSMB will also review all SAEs. Dr. Welge, the project statistician, will be responsible for providing updated safety data to the DSMB prior to each meeting. The DSMB will provide a written report of their recommendation as to whether the study should continue, be modified, or should be terminated.

6. Communication plan to IRB and NIDA: Dr. Winhusen, in conjunction with the DSMB, will be responsible for making certain that the DSMB files their report to the IRB as well as to the sponsor (NIDA) of the study.