Study Title: NIDA CTN Protocol 0150: Personally-Tailored Opioid-overdose and Medicaton for opioid use disorder (MOUD) Educaton (TOME) for pregnant and postpartum persons in MOUD: A pilot randomized trial (TOME trial)

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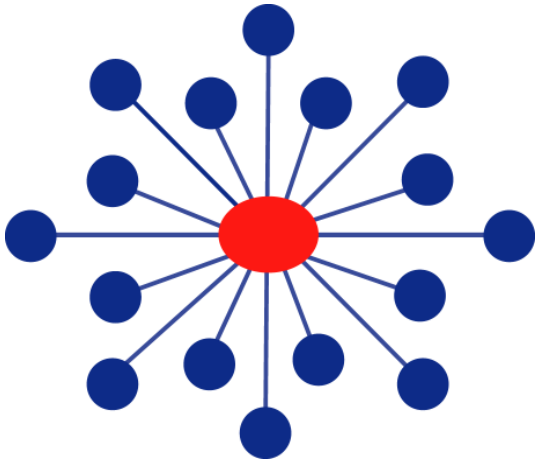

NIDA CTN Protocol 0150

Personally-Tailored Opioid-overdose and Medication for opioid use disorder (MOUD) Education (TOME) for pregnant and postpartum persons in MOUD: A pilot randomized trial (TOME trial)

Lead Investigator: T. John Winhusen, PhD
Protocol Managers: Frankie Kropp, MS and Lindsay Bybee, MA

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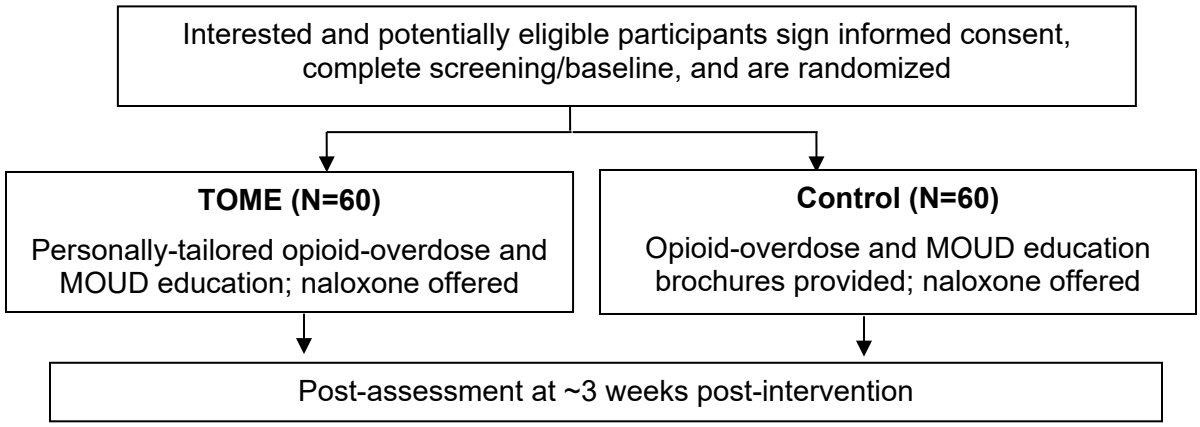
1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
BUP	Buprenorphine
CCTN	Center for Clinical Trials Network
CoC	Certificate of Confidentiality
CRF	Case report form
CTN	Clinical Trials Network
DSMB	Data and Safety Monitoring Board
GCP	Good Clinical Practice
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional review board
ITT	Intent-to-Treat
LI	Lead Investigator
MOUD	Medication for opioid use disorder
NIDA	National Institute on Drug Abuse
OHRP	Office for Human Research Protections
OOTAS	Opioid Overdose & Treatment Survey
OUD	Opioid use disorder
OVN	Ohio Valley Node
PI	Principal Investigator
PP	Pregnant and postpartum
PRISM	Psychiatric Research Interview for Substance and Mental Disorders
QA	Quality Assurance
RA	Research assistant
RCT	Randomized controlled trial
SAE	Serious Adverse Event
SAMHSA	Substance Abuse and Mental Health Services Administration
SOP	Standard Operating Procedure
SUD	Substance Use Disorder
TOME	Personally-Tailored Opioid-overdose and Medication for opioid use disorder (MOUD) Education
UC	University of Cincinnati

2.0 STUDY SCHEMA

Figure 1. Study Schema



3.0 STUDY SYNOPSIS

3.1 Study Objectives

CTN-0150 includes two objectives:

- Primary Objective: To evaluate the ability of the Personally-Tailored Opioid-overdose and Medication for opioid use disorder (MOUD) Education (TOME) intervention to increase MOUD and opioid-overdose knowledge in pregnant and postpartum (PP) persons.
- Secondary Objective: To evaluate the ability of TOME to decrease MOUD-related internalized stigma and expected difficulty in avoiding drug use.

3.2 Study Design

This is an intent-to-treat, two-arm, open-label, randomized controlled trial. Eligible participants will be randomized in a 1:1 ratio to TOME or Control, balancing on site. Participants will receive the assigned intervention following randomization and will complete a three week follow-up assessment.

3.3 Study Population

Approximately 120 PP persons will be randomized into the trial. CTN is conducting the Medication treatment for Opioid-dependent expectant Mothers (MOMs; CTN-0080) trial to compare mother and infant outcomes of pregnant persons with OUD treated with extended-release buprenorphine (BUP), relative to sublingual BUP. This study will be conducted with six CTN-0080 sites with sufficient census to randomize approximately four participants per month. Eligible participants will be pregnant or within 12 months postpartum and will be enrolled in MOUD treatment.

3.4 Treatments

All randomized participants will be offered naloxone. All participants will complete an opioid-overdose and MOUD knowledge assessment during baseline. TOME participants will be offered a 15-minute intervention in which a trained research staff member reviews personal feedback reports with the recipient to provide information on the items missed on the knowledge assessment. Control participants will be offered three SAMHSA handouts: 1) “Opioid Overdose Prevention Toolkit: Safety Advice for Patients and Family Members”; 2) “Opioid Overdose Prevention Toolkit: Recovering from Opioid Overdose”; and 3) “Medication-Assisted Treatment for Opioid Addiction: Facts for Families and Friends”.

3.5 Assessments

The primary outcome is MOUD knowledge score. The key secondary outcome is opioid-overdose knowledge score. The baseline and 3-week follow-up assessments will ideally occur at the clinic site; however, these visits may occur in whole or in part via telemedicine, at other institutionally-affiliated clinical sites, or elsewhere in the community (including, but not limited to, home visits or other community sites affording appropriate safety and confidentiality) as permitted by the institution and other regulatory bodies.

3.6 Primary Analysis

Baseline-Week-3 difference in MOUD knowledge will be tested using linear regression at the 5% Type I error rate (two-sided) for the intent-to-treat population.

4.0 BACKGROUND AND RATIONALE

From 2010 to 2017, opioid-related maternal deaths increased by 220%.[1] Drug overdose deaths, particularly deaths involving synthetic opioids like fentanyl, reached record highs in 2020 and 2021;[2] drug overdose is now a leading cause of pregnancy-associated mortality in the United States.[3] Interventions to decrease overdose risks in pregnant and postpartum (PP) persons are lacking and are needed in order to address the epidemic of opioid-related overdoses.[3] Our team has developed and tested a brief personally-tailored opioid overdose prevention education and naloxone distribution (PTOEND) intervention that can be administered by bachelor's level staff.[4,5] Our PTOEND intervention was designed to expand harm reduction by not only encouraging the use of naloxone but also educating individuals about factors that increase risk for opioid-overdose, including modifiable behaviors that increase risk. In addition, the PTOEND was designed to promote medication for opioid use disorder (MOUD) engagement, which is effective for preventing opioid-overdoses[6,7] but is underutilized,[8] in part due to inaccurate perceptions including misconceptions about its side effects and lack of efficacy.[9-11] The results of a pre-post study of PTOEND suggested that it significantly increased opioid-overdose and MOUD knowledge and increased treatment readiness in out-of-treatment adult illicit opioid users having experienced an opioid-overdose.[5] In addition, the MOUD education intervention was found to significantly decrease expected difficulty in avoiding drug use;[5] which is important since improved self-efficacy has been associated with improved substance use outcomes.[12]

The initial study of PTOEND was with out-of-treatment active opioid users but it is also applicable for people enrolled in MOUD. First, while MOUD significantly decreases the risk of opioid-overdose, people enrolled in MOUD still overdose and the risk of overdose is heightened when MOUD is discontinued.[13] Opioid-overdose education, including information about risk factors for overdose, has been found to decrease overdose-risk behaviors[5] and, thus, would be expected to reduce opioid-overdose risk in individuals who continue to use illicit opioids while enrolled in MOUD or who relapse when they stop MOUD treatment. Second, the elements of PTOEND that increased readiness for MOUD should also serve to improve engagement and retention in MOUD. While the optimal length of MOUD has not been determined, a 6-month minimum is recommended.[14-16] Six month MOUD retention estimates vary but research suggests an estimated 6-month retention rate of 50% for methadone[17] and < 50% for buprenorphine.[18] There is consensus that retention needs to be improved but no evidence-based interventions for increasing MOUD retention have been established.[19] Stigma is one of the most commonly cited barriers to MOUD retention by individuals with OUD.[20-22] The PTOEND, which corrects stigma-eliciting misperceptions (e.g., MOUD is "just replacing one drug with another", etc.), is hypothesized to reduce internalized stigma. Another common barrier to MOUD engagement/ retention is inaccurate perceptions of MOUD – including myths about its side effects and lack of efficacy.[21] We evaluated the impact of the MOUD education component in a small (N=20) pre-post study of recently-enrolled MOUD patients and found a significant increase in MOUD knowledge after MOUD education ($p<.01$). PTOEND has been found to increase patient's belief in their ability to avoid drug use, which may be the result of correcting MOUD myths, including providing information about its effectiveness.[5]

The present trial will test a modified version of the PTOEND intervention, referred to as the personally-Tailored Opioid-overdose and MOUD Education (TOME) intervention, in pregnant and postpartum (PP) persons. Modifications include updating the knowledge assessment/education to reflect changes in the drug supply (i.e., the current high prevalence of fentanyl and increasing prevalence of xylazine) and the addition of items specific to pregnancy.

5.0 STUDY OBJECTIVES

5.1 Primary Objective

The primary objective of this study is to evaluate the ability of TOME to increase MOUD and opioid-overdose knowledge in PP persons.

5.2 Secondary Objective

The secondary objective is to evaluate the ability of TOME to decrease MOUD-related internalized stigma and expected difficulty in avoiding drug use.

6.0 STUDY DESIGN

6.1 Overview of Study Design

This is an intent-to-treat, two-arm, open-label, randomized controlled trial. Eligible participants will be randomized in a 1:1 ratio to TOME or Control, balancing on site. Participants will receive the assigned intervention following randomization and will complete follow-up assessments at~ 3 weeks post-randomization. Key outcome measures are: 1) MOUD knowledge (primary); and 2) opioid-overdose knowledge (key secondary).

6.2 Number of Sites and Participants

Approximately 120 participants, recruited from approximately 6 sites, will be randomized into the trial. Patients enrolled in MOUD (either buprenorphine or methadone) at the study site who are either pregnant or within 12 months postpartum will be recruited for the study. Participants may be recruited from a variety of other sources, including advertising if needed. Recruitment advertisements will be approved by the Institutional Review Board (IRB). Efforts will be made to recruit a study sample that reflects, or exceeds, the proportion of minorities in treatment at the sites.

6.3 Study Duration

Enrollment is expected to take place over a period of approximately 6 months. Duration of study participation will be approximately 3 – 4 weeks.

6.4 Site and Participant Selection

6.4.1 Site Selection

CTN is conducting the Medication treatment for Opioid-dependent expectant Mothers (MOMs; CTN-0080[23]) trial to compare mother and infant outcomes of pregnant persons with OUD treated with extended-release buprenorphine (BUP), relative to sublingual BUP. CTN-0080 has completed recruitment but has a very long active treatment phase (i.e., through 12 months post-partum). Staff need to be retained through the CTN-0080 active treatment phase. The proposed study would be conducted with six CTN-0080 sites with sufficient census to enroll randomize approximately four participants per month.

6.4.1.1 *Site Characteristics*

Participating sites should:

1. have been a site in CTN-0080;
2. have sufficient census to meet the target randomization of 4 per month

6.4.2 Participant Selection

6.4.2.1 *Inclusion Criteria*

Potential participants must be:

1. 18 years of age or older;
2. pregnant or be within 12 months postpartum;

3. enrolled in MOUD (either buprenorphine or methadone) at the study site or affiliated clinic where enrollment can be confirmed;
4. able to understand the study, and having understood, provide written informed consent in English

6.4.2.2 *Exclusion Criteria*

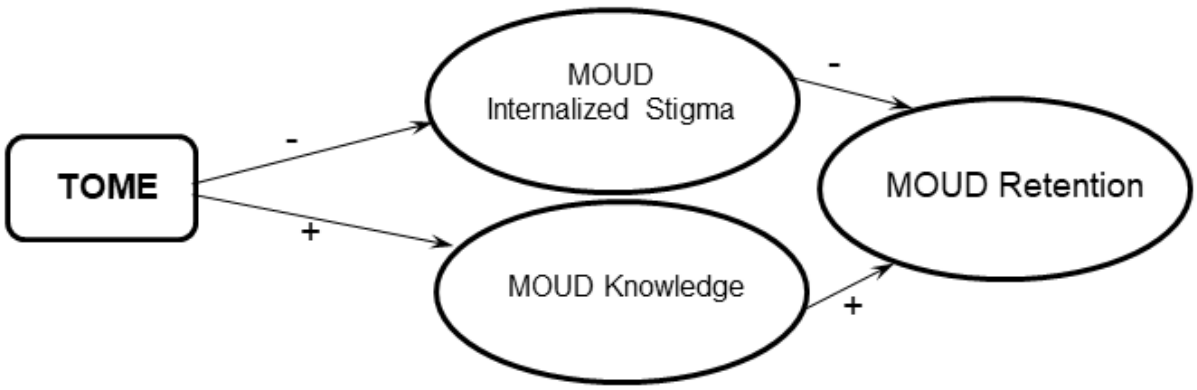
Potential participants must not:

1. have suicidal or homicidal ideation requiring immediate attention
2. be currently in jail, prison, or any inpatient overnight facility as required by court of law or have pending legal action

6.5 Potential Follow-up Trial

The conceptual model for TOME's hypothesized ability to increase MOUD treatment retention is provided in Figure 2. The present pilot trial is being conducted with active CTN-0080 study sites and is limited to the time remaining for CTN-0080 implementation. As a consequence, the pilot trial is limited to a 3-week follow-up and, thus, is not testing TOME's ability to increase MOUD retention. Instead, this pilot trial is testing TOME's impact on the two hypothesized mediators by which TOME would improve retention. Finding that TOME significantly increases MOUD knowledge and significantly decreases MOUD stigma would provide support for a follow-up trial to test TOME's ability to improve MOUD retention rates.

Fig. 2: Conceptual Model of TOME's Retention Impact



7.0 STUDY MEASURES

7.1 Key Outcome Measures of the Primary Objective

7.1.1 Primary Outcome - MOUD knowledge score

The primary outcome is MOUD knowledge as measured by the Opioid Overdose and Treatment Awareness Survey (OOTAS) knowledge evaluation. The OOTAS is comprised of 4 sections: 1) opioid-overdose risk factors; 2) signs of an opioid-overdose; 3) how to respond to an opioid-overdose; and 4) misconceptions about MOUD.[4] The OOTAS has been successfully used to measure MOUD knowledge and knowledge change in two published studies[4,5] and in a small (N=20) pre-post study of recently-enrolled MOUD patients, which found a significant increase in MOUD knowledge after MOUD education ($p<.01$). For the present trial, the OOTAS has been modified to include two additional questions specific to pregnancy (i.e., are methadone and BUP recommended during pregnancy and can babies be born addicted as a result of taking methadone or BUP during pregnancy). The modified OOTAS includes 10 true-false questions to assess MOUD knowledge, yielding a potential score of 0-10.

7.1.2 Key Secondary Outcome – Opioid-overdose knowledge score

The key secondary outcome is opioid-overdose knowledge as measured by the first three sections of the OOTAS. The OOTAS has been successfully used to measure opioid-overdose knowledge and knowledge change in two prior studies conducted with individuals with OUD. For the present trial, the OOTAS has been modified to include two additional questions to assess the participant's knowledge of the increase risk of opioid-overdose with fentanyl and potential increased risk with xylazine. The modified OOTAS includes 31 true-false questions to assess opioid-overdose knowledge, yielding a potential score of 0-31.

7.2 Secondary Outcome Measures

7.2.1 MOUD Internalized Stigma

The Methadone Maintenance Treatment Stigma Mechanisms Scale (MMT-SMS) is a self-report questionnaire assessing three dimensions of stigma: anticipated, enacted, and internalized stigma.[24] The MMT-SMS has demonstrated good internal consistency and validity.[24] The MOUD education is expected to decrease internalized stigma by countering stigma-inducing myths (e.g., methadone/BUP is just replacing one drug with another, etc.) and, thus, the internalized stigma score is the outcome of interest. The MMT-SMS was designed for use with any MOUD medication and the wording will be modified to assess stigma related to the medication that the participant is receiving.

7.2.2 Drug Self-efficacy

Self-efficacy in avoiding drug use will be assessed with the Thoughts about abstinence (TAA) instrument.[25] This measure assesses the participant's desire to quit, expected success in quitting and estimated difficulty in avoiding drug use.[25] Our MOUD education intervention has been found to increase expected success in avoiding drug use as measured by the TAA.[5]

7.3 Safety Measures of the Primary Objective

7.3.1 Adverse Events (AEs)

There are not specific guidelines for adverse event (AE) and serious adverse event (SAE) reporting for behavioral trials but it is important to assess for potential AEs that could result from exposure to a behavioral intervention.[26] TOME is a low-risk intervention but staff will assess for two AEs that would be of clinical import: 1. Suicidal ideation and 2. Homicidal ideation. Research suggests that using the FDA definition of 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) for behavioral trials with substance using populations does not produce meaningful safety information in that many SAEs are reported but none judged to be related to the intervention.[27] SAEs will only be reported for events related to a study-defined AE (e.g., hospitalization due to suicidal ideation, etc.).

7.4 Other Measures

7.4.1 Screening Assessments

Pre-screen Interview: The pre-screen interview will include questions about pregnancy/ postpartum status and enrollment in MOUD treatment.

Demographics: Items from the PhenX Tier 1 of the Substance Abuse and Addiction core[28] will be used to collect information on demographic characteristics.

Suicidal and Homicidal Screening Form (PRISM): The Suicide and Homicide Screening Form is a structured, reliable interview modified from the Psychiatric Research Interview for Substance and Mental Disorders- PRISM[29] and will be completed by study staff during screening/baseline. A qualified mental health professional must assess participants reporting current suicidal/ homicidal intent as specified in the site clinical SOP. For visits held via telemedicine or at an external location, research staff will contact a qualified clinician via phone to coordinate an assessment via telemedicine as quickly as possible; ideally this assessment will occur while the staff and participant are together at the external location.

Treatment and Perinatal Status: The Treatment and Perinatal Status form will be used to assess study candidates' status on study inclusion/exclusion criteria related to pregnancy / postpartum status and enrollment in MOUD treatment.

Prisoner Status: The Prisoner Status form will be used to assess study candidates' status on the study exclusion criterion related to prisoner status.

7.4.2 Sample Characteristics

Substance use history: Participants will be asked the frequency with which they used alcohol, tobacco, and other drugs of abuse during their last active period of use. The wording for the assessment will be taken from the NIDA-Modified ASSIST V2.0, which is a modified version of the World Health Organization Alcohol, Smoking, and Substance Involvement Screening Test.[30]

7.5 Administrative Forms

Locator Form(s): A locator form is used to obtain information to assist in finding participants during the study. This form is completed at the Screening/Baseline/Randomization visit and collects

contact information including the participant's current address, email address, phone numbers, etc. In order to facilitate locating participants if direct contact efforts are unsuccessful, addresses and phone numbers of family/friends who may know how to reach the participant are collected along with releases of information. No information from locator forms is used in data analyses.

Study Eligibility: This form, which lists all the study inclusion and exclusion criteria, must be completed for every participant who has signed informed consent. Eligible participants will be randomized; ineligible participants will be excluded and deemed screen failures.

Study Intervention Provided: This form must be completed for every randomized participant. The purpose of the form is to capture the elements of the study intervention provided to the participant (e.g., naloxone provided, etc.).

Study Completion: This form, which indicates that the participant has formally terminated his/her study involvement, must be completed for every participant who has been randomized into the study. The purpose of the Study Completion Form is to document: 1) the date on which a randomized participant attended their final study visit, 2) whether the participant completed the study or ended study involvement prematurely, and 3) if the participant ended study involvement prematurely, the reason why that occurred. This form also provides a location for the site PI attestation of review of all study data.

Protocol Deviation: This form should be entered into REDCap whenever a protocol deviation occurs. This form will document a description of the deviation, how it occurred, the corrective action taken to resolve the specific deviation, as well as a description of the plan implemented to prevent future occurrences of similar deviations.

Mental Health Follow-up Assessment: This assessment must be completed by a qualified clinician if the participant endorses suicidality or homicidality in response to the AE assessment. The completion of the Mental Health Follow-up Assessment form requires direct evaluation of the participant for suicide/homicide risk by a qualified mental health professional according to the site's specific SOP. This evaluation will ideally take place prior to the participant leaving the study visit. For visits held via telemedicine or at an external location, research staff will contact a qualified clinician via phone to coordinate an assessment via telemedicine as quickly as possible; ideally this assessment will occur while the staff and participant are together at the external location.

8.0 STUDY PROCEDURES

8.1 Study Overview

The schedule of research visits and research assessments for all participants is delineated in ***Table 1***. In accordance with the site's institutional policies and procedures, study visits may occur at other locations affiliated with the institution or elsewhere in the community (including, but not limited to, home visits or visits at non-affiliated community sites), or via remote contact, such as by telephone or other institutionally-approved telemedicine mechanisms. All visits occurring outside of the primary research study site will be managed in such a way that there is no increased risk to participant safety.

8.2 Participant Recruitment, Pre-screening, and Consent

Potential participants will be primarily recruited from existing clients at participating sites. Advertisements may be used, as needed, but all participants must have completed intake at a study site to be eligible for randomization. Interested candidates will complete a pre-screen, which will include questions about pregnancy/postpartum and MOUD treatment status. Candidates who pass the pre-screen will be scheduled for a visit to complete the informed consent, screening/baseline, and randomization. The consent procedure will occur during a live interaction between the candidate and study staff; however, this interaction may occur face-to-face at the study site or at another approved location, or via telemedicine in accordance with institutional policies. If still interested after receiving an explanation of the study, the candidate will be given an opportunity to review, inquire about, and sign the informed consent form. Any participant who has difficulty understanding the information contained in the consent form will be asked to review the misunderstood portion(s) of the consent and discuss them with a research staff member until they show complete understanding of the information and may thus give full consent. Research staff members will work closely with the study candidates in an effort to help them understand the requirements of their participation. Persons with literacy problems will be assisted to the extent possible. Any participant who is unable to demonstrate understanding of the information contained in the informed consent will be excluded from study participation. In the event that the consent procedure occurs via telemedicine, the candidate will provide consent via a HIPAA-compliant electronic system or will be provided with a prepaid shipper/envelope for returning the signed consent to the study team. No other study procedures will occur until the signed consent is received back from the candidate.

8.3 Screening/Baseline

After signing the informed consent form, the study participant will proceed through screening/baseline, which should be completed within a single session.

8.4 Randomization Plan

Eligible participants will be randomized in a 1:1 ratio, stratified by site, to TOME or Control. Research staff will randomize participants to the TOME or Control arm, using REDCap's randomization module; the randomization sequence will be unknown to the research staff.

Table 1: Overview of Assessments and Procedures			
Research Visits	**Screen/baseline/ randomization**	**Week 3 visit**	**As Needed**
Screening Assessments			
Pre-screen interview	X		
Informed Consent	X		
Demographics	X		
Treatment and Perinatal Status	X		
Prisoner Status	X		
PRISM-Suicide/Homicide	X		
Sample Characteristics			
Substance use history	X		
Safety Assessments			
Adverse events		X	
Efficacy Assessments			
Opioid Overdose and Treatment Awareness Survey (OOTAS)	X	X	
Methadone Maintenance Treatment Stigma Mechanisms Scale (MMT-SMS	X	X	
Thoughts about abstinence	X	X	
Administrative Forms			
Locator information form	X		
Study Eligibility	X		
Study Intervention Provided	X		
Study Completion			X
Protocol Deviation			X
Mental Health Follow-up Assessment			X

8.5 Participant Reimbursement

Participants will be reimbursed for their transportation, inconvenience, and time. The form of this reimbursement will be determined by the study sites. Participants will be reimbursed $45 for completing screening/baseline and $30 for completing the Week 3 visit.

8.6 Trial Discontinuation

The study sponsor has the right to discontinue the investigation at any time.

9.0 STUDY TREATMENTS

All randomized participants will be offered naloxone.

9.1 TOME

The TOME intervention is a modified version of the PTOEND intervention.[5] Modifications include updating the knowledge assessment/education to reflect changes in the drug supply (i.e., the current high prevalence of fentanyl and increasing prevalence of xylazine) and the addition of items specific to pregnancy. Like PTOEND, TOME is a computer-guided intervention which utilizes REDCap[31] to complete assessments and automatically generate personally-tailored feedback reports; the use of REDCap, which is an NIH-supported, secure, web-based research data platform, limits the technological costs of the intervention to the cost of an internet connection and a computer tablet.

TOME entails a trained RA: 1) administering a REDCap survey to assess an individual's opioid-overdose /MOUD knowledge; and 2) reviewing the personal feedback reports with the recipient. In the present study, the REDCap survey will be administered to all participants at baseline with only the TOME participants receiving the personal feedback reports. Opioid-overdose /MOUD knowledge is assessed with the OOTAS; see Winhusen et al[4] for information about the survey. In brief, the OOTAS is comprised of 4 sections: 1) opioid-overdose risk factors; 2) signs of an opioid-overdose; 3) how to respond to an opioid-overdose; and 4) misconceptions about MOUD. The first 3 sections include only evidence-based items supported by a literature review, while items for the fourth section were based on both a literature review and on input from the medical staff of the University of Cincinnati-affiliated methadone program. For the present trial, the OOTAS has been modified to include four additional questions: two to assess the participant's knowledge of the increased risk of opioid-overdose with fentanyl and possible increased risk with xylazine and two MOUD knowledge questions specific to pregnancy (i.e., are methadone and BUP recommended during pregnancy and can babies be born addicted as a result of taking methadone or BUP during pregnancy). The Opioid Overdose & Treatment Survey (OOTAS) Feedback Report is generated from the OOTAS and includes a section corresponding to each of the four sections of the OOTAS. The report provides feedback on the questions answered incorrectly by the participant to provide targeted knowledge enhancement, including the correction of misconceptions about MOUD. TOME participants will be offered a copy of their personalized OOTAS Feedback Report; either a physical or electronic copy may be provided.

Training: Trainees will receive a training manual. Training sessions will provide didactic training on the background and rationale of the study, basic listening strategies, a review of the personalized OOTAS Feedback Report, and specific instruction on delivery of the TOME.

9.2 Control

Participants randomized to the control condition will be offered three SAMHSA handouts: 1) "Opioid Overdose Prevention Toolkit: Safety Advice for Patients and Family Members";[32] 2) "Opioid Overdose Prevention Toolkit: Recovering from Opioid Overdose";[33] and 3) *"Medication-Assisted Treatment for Opioid Addiction: Facts for Families and Friends"*.[34] These handouts can be offered as physical copies or electronically.

10.0 ANALYTICAL PLAN

10.1 Statistical Hypotheses for Primary Objective

10.1.1 Key Hypotheses

It is hypothesized that the TOME, relative to the control, group will have a greater increase in: 1) MOUD knowledge (primary); and 2) opioid-overdose knowledge (key secondary).

10.1.2 Secondary Hypotheses

It is also hypothesized that the TOME, relative to the control, group will have a significantly greater decrease in: 1) internalized stigma and 2) estimated difficulty in avoiding drug use.

10.2 Intent-to-Treat Participant Population

The intent-to-treat (ITT) population is defined as the participants who are randomized.

10.3 Analysis Plan

Each outcome measure will be analyzed for the intent-to-treat population. All statistical tests will be conducted at the 5% Type I error rate (two-sided). All regressions will use outcome as the response variable, treatment (TOME vs. Control) as the covariate of interest, and baseline outcome as a supporting covariate. Site and site-by-treatment will be initially included as supporting covariates and dropped if they are not significant. Baseline-Week-3 continuous outcomes such as the difference in MOUD knowledge will be tested using linear regressions. The Pearson Chi-Square test will be used to test for treatment group differences in AEs.

10.4 Sample Size Analysis

In our published PTOEND pre-post study we were able to detect a statistically significant increase in opioid-overdose and MOUD knowledge with 80 enrolled participants.[5] In an unpublished pre-post evaluation of the MOUD education component in patients recently enrolled in MOUD (either buprenorphine or methadone), a sample size of 40 was sufficient to detect a statistically significant increase in mean correct responses from baseline (6.1, SD=1.5) to post-PTOEND (7.3, SD=1.1). Assuming a two-sided test, an $\alpha = .05$, that ≥88% of enrolled participants attend the week 3 visit, and mean correct post-intervention responses of 7.3 for the TOME and 6.7 for the Control group, the target sample size of 120 will provide 80% power to detect the difference as statistically significant.

10.5 Interim Analyses

This trial has a relatively short recruitment period (approximately 6 months) and no interim analyses are planned.

10.6 Minority/Sex Analyses

In accordance with National Institutes of Health guidelines, modelling of the key outcomes will be completed to determine whether treatment response was significantly affected by participant minority status using an interaction term between treatment arm and minority status being considered.

10.7 Post-hoc Analyses

In addition to the analyses described above, a number of post-hoc analyses may be completed. An example of a possible analysis includes an exploration of participant screening/baseline variables that are predictive of outcome.

11.0 REGULATORY COMPLIANCE, REPORTING, AND MONITORING

11.1 Regulatory Compliance

Written approval by the Institutional Review Board (IRB) of record for the study protocol, consent form, other supporting documents, and any advertising for participant recruitment will be provided to the sites prior to being utilized in the study. Any amendments to the protocol or consent materials must be approved by the IRB of record before they are implemented. Unanticipated problems involving risk to study participants will be promptly reported to, and reviewed, by the IRB of record, according to its usual procedures. Annual progress reports and local SAE reports will be submitted to the IRB, according to its usual procedures.

The study will be registered and updated as needed in www.ClinicalTrials.gov.

11.2 Statement of Compliance

This study will be conducted in accordance with the current version of the protocol, in full conformity with the ethical principles outlined in the Declaration of Helsinki, the Regulations for the Protection of Human Subjects codified in the International Council for Harmonisation GCP Guidelines, and all other applicable regulatory requirements. An Operations Manual will be provided as a reference guide and study quality assurance tool.

11.3 Institutional Review Board Approval

Per NOT-OD-16-094, the University of Cincinnati IRB (UC IRB) will be the IRB of record for the protocol and will provide study oversight in accordance with 45 CFR 46. Participating institutions will be asked to agree to rely on the UC IRB and will enter into reliance/authorization agreements for Protocol CTN-0150, as needed. The UC IRB will follow written procedures for reporting its findings and actions to appropriate officials at each participating institution.

Prior to initiating the study, the lead team will ensure that the local IRB at each site has entered into a reliance/authorization agreement with the IRB of record (UC IRB) and that written IRB approval has been secured from the IRB of record for each site involved. If changes to the study protocol become necessary, protocol amendments will be submitted in writing for approval by the IRB of record prior to implementation. In addition, the IRB of record will approve all consent forms, recruitment materials, any materials given to the participant, and any changes made to these documents throughout study implementation. For changes to the consent form, a decision will be made regarding whether previously consented participants need to be re-consented. IRB continuing review will be performed annually. Each site principal investigator (PI) is responsible for maintaining copies of all current IRB approval notices, IRB-approved consent documents, and approval for all protocol modifications. These materials must be received by the investigator prior to the initiation of research activities at the site and must be available at any time for audit.

11.4 Regulatory Files

Essential documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements. The regulatory files should contain all essential documents, other required regulatory documents, study-specific documents, and all important communications.

11.5 Informed Consent

The informed consent form is a means of providing information regarding the trial to a prospective participant and allows for an informed decision about participation in the study. Informed consent continues throughout the individual's study participation. Each study site must have the study informed consent approved by the UC IRB. Prior to initial submission to the IRB the consent form must be sent to the Lead Node to confirm that each consent form contains the required elements of informed consent as delineated in 21 CFR 50.25(a) and CFR 46.116(b), pertinent additional elements detailed in 21 CFR 50.25(b) and 45 CFR 46.116(c), and any applicable Center for Clinical Trials Network (CCTN) requirements. Every study participant is required to sign a valid, IRB-approved, current version of the study informed consent form prior to the initiation of any study related procedures. The site must maintain the original signed informed consent for every participant in a locked, secure location that is in compliance with all applicable IRB and institutional policies and that is accessible for quality assurance and study monitor review. Every study participant should be given a copy of the signed consent form.

Prior to signing the informed consent form, research staff who are knowledgeable about the study will explain the study to the potential participant and provide the participant with a copy of the consent to read during the consent process and to keep for reference. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and their rights as research participants. Extensive discussion of risks and possible benefits will be provided to the participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. If the participant is interested in participating in the study, a researcher who is authorized by the PI to obtain informed consent and approved by the UC IRB, will review each section of the informed consent form in detail, answer any of the participant's questions, and determine if the participant comprehends the information provided by administering the comprehension tool. The participant will consent by signing and dating the consent documents. The person obtaining consent will also sign and date the consent document. The consent must be properly executed and complete to be valid. It is strongly recommended that another research staff member review the consent after it is signed to ensure that the consent is properly executed and complete.

Staff members delegated by the PI to obtain informed consent must be listed on the Delegation of Responsibility and Staff Signature Log. All persons obtaining consent must have completed appropriate GCP and Human Subjects Protection training, as mandated by NIDA standard operating procedures.

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

11.6 Participant and Data Confidentiality

Confidentiality will be maintained in accordance with all applicable federal regulations and/or state/Commonwealth law and regulations. By signing the protocol signature page, the investigator affirms that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB of record; affiliated institution; and employees only

under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees.

This study will be covered by a federal Certificate of Confidentiality (CoC), which protects identifiable research information from forced disclosure. This protects participants against disclosure of sensitive information (e.g., drug use). The CoC allows the investigator and others who have access to research records to permanently refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level, excepting certain circumstances.

By protecting researchers and institutions from being compelled to disclose information that would identify research participants, the CoC helps achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants. Participant records will be held confidential by the use of study codes for identifying participants on CRFs, secure storage of any documents that have participant identifiers, secure transport of study documents while performing study visits at any off-site location, and secure computing procedures for entering and transferring electronic data.

11.6.1 Health Insurance Portability and Accountability Act (HIPAA)

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

11.7 Investigator Assurances

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

11.7.1 Financial Disclosure/Conflict of Interest

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

11.8 Quality Assurance Monitoring

In accordance with federal regulations, the study sponsor is responsible for ensuring proper monitoring of a clinical trial and ensuring that the trial is conducted in accordance with the protocol. Qualified monitors will oversee aspects of site conformity to make certain the site staff is operating within the confines of the protocol, and in accordance with GCP. This includes but is not limited to protocol compliance, documentation auditing, and evaluating whether the informed consent

process is being correctly followed and documented. Non-conformity with protocol and federal regulations can be reported as a protocol deviation and submitted to the study sponsor and study IRB for further review.

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

11.9 Prisoner Certification

As per 45 CFR 46 Subpart C, there are additional protections pertaining to prisoners as study participants. A prisoner is defined as any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing. Prisoners will not participate in the present study.

11.10 Protections for Pregnant Women, Fetuses, and Neonates

As per 45 CFR 46 Subpart B, there are additional protections pertaining to pregnant women, fetuses, and neonates involved in research. Pregnancy encompasses the period of time from implantation until delivery. Fetus is defined as the product of conception from implantation until delivery. In order to meet these additional protections, study staff will abide by conditions outlined in 45 CFR 46.201-206. Potential participants will be fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.

11.11 Records Retention and Requirements

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

11.12 Reporting to Sponsor

The site PIs agree to submit accurate, complete, legible and timely reports to the Sponsor, as required. These include, but are not limited to, reports of any changes that significantly affect the conduct or outcome of the trial or increase risk to study participants. At the completion of the trial, the LI will provide a final report to the Sponsor.

11.13 Audits

The Sponsor has an obligation to ensure that this trial is conducted according to GCP guidelines and may perform quality assurance audits for protocol compliance. The LI and authorized staff

from the Ohio Valley Node; the National Institute on Drug Abuse Clinical Trials Network (NIDA CTN, the study sponsor); monitors from the site's local Node, and other agencies such as the HHS, the OHRP and the IRB of record may inspect research records for verification of data, compliance with federal guidelines on human participant research, and to assess participant safety.

11.14 Study Documentation

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

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

11.15 Protocol Deviations

Any departure from protocol-specified procedures and requirements will be classified as either a major or minor protocol deviation. The difference between a major and minor protocol deviation has to do with the seriousness of the event and the corrective action required. A minor protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Major protocol deviations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria, or the integrity of study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Sites will be responsible for developing corrective action plans for both major and minor deviations as appropriate. Those corrective action plans may be reviewed/approved by the Lead Node with overall approval by the IRB of record. All protocol deviations will be monitored at each site for (1) significance, (2) frequency, and (3) impact on the study objectives, to ensure that site performance does not compromise the integrity of the trial. Departures from SOPs not detailed within the protocol will not be considered to be protocol deviations.

Protocol deviations will be recorded in REDCap via the Protocol Deviation CRF. The LI must be contacted immediately if an unqualified or ineligible participant is randomized into the study or if another major protocol deviation occurs.

Each site is responsible for reviewing the IRB of record's definition of a protocol deviation (minor deviation) or violation (major deviation) and understanding which events need to be reported to the IRB of record, and when reporting is to be done. Sites must recognize that the CTN and IRB definition of a reportable event may differ and act accordingly in following all reporting requirements for both entities.

11.16 Safety Monitoring

11.16.1 Data and Safety Monitoring Board (DSMB)

The MOMs trial has a NIDA CTN DSMB that is responsible for conducting periodic reviews of accumulating safety, trial performance, and outcome data. Given the low risk associated with the TOME intervention and the brevity of the study time frame, a separate DSMB was not established for the TOME trial. Instead, should Dr. Winhusen feel the need for DSMB input (e.g., as the result of an AE or SAE etc.) he will request an ad hoc meeting with the MOMs DSMB.

11.16.2 Adverse Events (AEs)

There are not specific guidelines for adverse event (AE) and serious adverse event (SAE) reporting for behavioral trials but it is important to assess for potential AEs that could result from exposure to a behavioral intervention.[26] TOME is a low-risk intervention but staff will assess for two AEs that would be of clinical import: 1. Suicidal ideation and 2. Homicidal ideation. Research suggests that using the FDA definition of 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) for behavioral trials with substance using populations does not produce meaningful safety information in that many SAEs are reported but none judged to be related to the intervention.[27] SAEs will only be reported for events related to an AE (e.g., hospitalization due to suicidal ideation, etc.). The study staff will be trained to monitor for and report AEs and SAEs. Additionally, as applicable, sites will submit reporting of AEs/SAEs according to IRB requirements. Each of the sites has established practices for managing medical and psychiatric emergencies, and the study staff will continue to utilize these procedures. Treatment providers at each site will be responsible for monitoring participants for possible clinical deterioration or other problems, and for implementing appropriate courses of action.

11.17 Training Requirements

A Training Plan will be developed to incorporate general training, study-specific training, mechanisms for competency assessment as well as a detailed description of training and supervision. The CTN-0150 study staff will be trained as specified in the study Training Plan. Training will include Human Subjects Protection and GCP as well as protocol-specific training on assessments, study interventions, safety and safety event reporting, study visits and procedures, data management, and quality assurance. The Lead Node is primarily responsible for development and delivery of study-specific training related to the study intervention(s) and procedures.

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

12.0 DATA MANAGEMENT AND PROCEDURES

12.1 Design and Development

The OVN will be responsible for development of eCRFs, development and validation of the study database, ensuring data integrity, and training site and participating research staff on applicable data management procedures. The remainder of this section provides an overview of the Data Management Plan associated with this protocol.

12.2 Site Responsibilities

The data management responsibilities of each individual site will be specified by the Lead Node.

12.3 Data Center Responsibilities

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

12.4 Data Collection

The data collection process consists of direct data entry by participants and research staff into the REDCap forms and surveys. Data entry into REDCap should be completed according to the instructions provided and project specific training. 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. For instance, validity checks will employ skip logic to ensure certain item sets are not available to respondents once initial responses are given. The investigator is responsible for maintaining accurate, complete, and up-to-date records, and for ensuring the completion of the eCRFs for each research participant.

12.5 Data Acquisition and Entry

Completed forms and electronic data should be entered into the data management system in accordance with the CRF Completion Guidelines established by the OVN. Only authorized individuals shall have access to electronic CRFs.

12.6 Database Transfer/Lock

Data will be transmitted by the OVN to the NIDA central data repository as requested by NIDA. The OVN will conduct final data quality assurance checks and “lock” the study database from further modification. The final analysis dataset will be returned to NIDA, as requested, for storage and archive. We will comply with the following policy regarding the preparation and transfer of the study data:

> “Data from CTN trials are posted 18 months after the final database lock or after the primary manuscript is published, whichever comes first. All of the data are de-identified, and only raw data (i.e., no analysis datasets or derived variables) are

provided. Data documentation, consisting of all annotated case report forms (CRFs), the data dictionary, and de-identification notes, is provided to users to assist in data interpretation. Protocol documentation, including a brief study description, the study protocol, and a link to the primary manuscript, is also provided, and users are encouraged to consult these documents for insight regarding proper interpretation of the data."

12.7 Data Training

The Training Plan for research staff includes provisions for training on assessments, eCRF completion guidelines, data management procedures, and the use of REDCap.

12.8 Data QA

To address the issue of data quality, the OVN will follow a standard data monitoring plan.

13.0 PUBLIC ACCESS AND DATA SHARING PLAN

This study will comply with the NIH Data Sharing Policy and Implementation Guidance (https://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm).

Primary data for this study will be available to the public in the NIDA data repository, per NIDA CTN policy. For more details on data sharing please visit https://datashare.nida.nih.gov/.

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

The planning, preparation, and submission of publications will follow the policies of the Publications Committee of the CTN.

14.0 PROTOCOL SIGNATURE PAGE

SPONSOR'S REPRESENTATIVE (CCTN SCIENTIFIC OFFICER OR DESIGNEE)

Printed Name	Signature	Date

ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version 1.3 of the protocol and agree to conduct this clinical study in accordance with the design and provisions specified therein.
- I agree to follow the protocol as written except in cases where necessary to protect the safety, rights, or welfare of a participant, an alteration is required, and the sponsor and IRB have been notified prior to the action.
- I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.
- I agree to personally conduct or supervise this investigation at this site and to ensure that all site staff assisting in the conduct of this study are adequately and appropriately trained to implement this version of the protocol and that they are qualified to meet the responsibilities to which they have been assigned.
- I agree to comply with all the applicable federal, state, and local regulations regarding the obligations of clinical investigators as required by the Department of Health and Human Services (HHS), the state, and the IRB.

SITE'S PRINCIPAL INVESTIGATOR

Printed Name	Signature	Date

Clinical Site Name _____

Node Affiliation _____

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16.0 Appendix: Data and Safety Monitoring Plan

16.1 Protocol Summary

16.1.1 Protocol Description

The present trial will test a modified version of the PTOEND intervention, referred to as the personally-Tailored Opioid-overdose and MOUD Education (TOME) intervention, in pregnant and postpartum (PP) persons. The primary objective of this study is to evaluate the ability of TOME to increase MOUD and opioid-overdose knowledge in PP persons. The secondary objective is to evaluate the ability of TOME to decrease MOUD-related internalized stigma and expected difficulty in avoiding drug use.

16.1.2 Key outcome measures

The primary outcome is MOUD knowledge score. The key secondary outcome is opioid-overdose knowledge score.

16.1.3 Inclusion/Exclusion Criteria:

Participant Inclusion Criteria

Potential participants must be:

1. 18 years of age or older;
2. pregnant or be within 12 months postpartum;
3. enrolled in MOUD (either buprenorphine or methadone) at the study site or affiliated clinic where enrollment can be confirmed;
4. able to understand the study, and having understood, provide written informed consent in English

Participant Exclusion Criteria

Potential participants must not:

1. have suicidal or homicidal ideation requiring immediate attention
2. be currently in jail, prison, or any inpatient overnight facility as required by court of law or have pending legal action

16.1.4 Sample Size

Approximately 120 PP persons will be randomized into the trial.

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16.2 Trial Management

1. List of participating enrolling clinics or data collection centers: The participating study sites are: 1) Gateway Community Services (Jacksonville, FL); 2) Marshall Health (Huntington, WV); 3) Medical University of South Carolina (Charleston, SC); 4) Pregnancy Recovery

Center/Magee Women's Hospital (Pittsburgh, PA); 5) SUPeRAD/ University of Utah Health System (Salt Lake City, UT); and 6) Vanderbilt University Medical Center (Nashville, TN).

2. Project timetable: This study will take approximately 15 months to complete which includes 4 months for protocol development, 2 months for pre-implementation, 6 months of active study implementation, and 3 months for closeout and data analysis.

3. Target population distribution: Based on the enrollment in the MOMs trial and the sites participating in TOME, the target population distribution is:

For the Targeted/Planned Enrollment Table	
Ethnic Category	**Female**
Hispanic or Latino (2%)	2
Not Hispanic or Latino (98%)	118
Unknown ethnicity	0
Ethnic Category All	120
Racial Categories	
American Indian/ Alaska Native (1%)	1
Asian (1%)	1
Native Hawaiian or Other Pacific Islander (0%)	0
Black or African American (7.7%)	9
White (83.8%)	101
Multirace (5.2%)	6
Racial unknown/other (1.3%)	2
Racial Categories Total	120

16.3 Data Management and Analysis

1. Data acquisition and transmission: Information will be obtained through REDCap, a web-based electronic data capture and management system. 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.
2. Data entry methods: 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.
3. Data analysis plan: All analyses will be completed on the intent-to-treat (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. No interim efficacy analyses or adaptive features are planned.

4. Efficacy Analyses:

   Each outcome measure will be analyzed for the intent-to-treat population. All statistical tests will be conducted at the 5% Type I error rate (two-sided). All regressions will use outcome as the response variable, treatment (TOME vs. Control) as the covariate of interest, and baseline outcome as a supporting covariate. Site and site-by-treatment will be initially included as supporting covariates and dropped if they are not significant. Baseline-Week-3 continuous outcomes such as the difference in MOUD knowledge will be tested using linear regressions. The Pearson Chi-Square test will be used to test for treatment group differences in AEs.

   Sample Size and Power: In our published PTOEND pre-post study we were able to detect a statistically significant increase in opioid-overdose and MOUD knowledge with 80 enrolled participants. In an unpublished pre-post evaluation of the MOUD education component in patients recently enrolled in MOUD (either buprenorphine or methadone), a sample size of 40 was sufficient to detect a statistically significant increase in mean correct responses from baseline (6.1, SD=1.5) to post-PTOEND (7.3, SD=1.1). Assuming a two-sided test, an $\alpha = .05$, that ≥88% of enrolled participants attend the week 3 visit, and mean correct post-intervention responses of 7.3 for the TOME and 6.7 for the Control group, the target sample size of 120 will provide 80% power to detect the difference as statistically significant.

5. Database lock and transfer: At the conclusion of data collection for the study, the OVN will perform final data cleaning activities and will "lock" the study database from further modification. De-identified versions of these datasets will also be provided to the NIDA CCTN-designated parties for posting on Datashare, as well as storage and archiving. We will comply with the following policy regarding the preparation and transfer of the study data:

   "Data from CTN trials are posted 18 months after the final database lock or after the primary manuscript is published, whichever comes first. All of the data are de-identified, and only raw data (i.e., no analysis datasets or derived variables) are provided. Data documentation, consisting of all annotated case report forms (CRFs), the data dictionary, and de-identification notes, is provided to users to assist in data interpretation. Protocol documentation, including a brief study description, the study protocol, and a link to the primary manuscript, is also provided, and users are encouraged to consult these documents for insight regarding proper interpretation of the data."

16.4 Quality Assurance

1. Procedures in place to ensure the validity and integrity of the data: Each site will be responsible for implementing management and oversight activities during the pre-initiation, implementation, and close-out phases. These activities will be conducted by local project management staff located at each site and aim to provide management support to the research team in order to ensure adherence to the protocol, SOPs, and regulatory requirements. The Lead Team will provide on-going monitoring of study progress and will hold regular study management meetings to monitor any emergent problems or ongoing problematic trends, and may additionally hold individual meetings with site staff in order to assist in resolving any site-specific problems that impact the study.

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.

16.5 Regulatory Issues

1. Reporting of adverse events (AEs) and serious adverse events (SAEs) to the IRB, NIDA, and the FDA: All study-defined SAEs will be reported to the participating site's IRB and NIDA within 72 hours of their discovery. This is a behavioral study and so FDA reporting is not required. All participant information will be de-identified when reporting SAEs. In a case where a reported SAE may be very severe and/or require a protocol amendment to be made, Dr. Winhusen may request an ad hoc review by the DSMB. All study-defined 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 IRBs and NIDA and the IRB's actions will then be reported to NIDA. Any other IRB actions 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 IRBs 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 may discontinue a participant from the trial if deemed clinically appropriate. NIDA has the right to discontinue the investigation at any time.
5. Disclosure of conflict of interest: The investigators have no conflicts of interest.

16.6 Trial Safety

1. Potential Risks and benefits for participants:

Risks:

- Breach of confidentiality: As with any study, there is a potential risk of loss of confidentiality. To maintain participant confidentiality, study records and data will be stored in compliance with the International Conference on Harmonization (ICH) guidelines. Participant-reported data will be collected through REDCap, which is HIPAA-compliant and 21 CFR Part 11- ready for audit trails for tracking data manipulation and exports. Emails or text messages between researchers and participants, used in retention efforts, will be deleted after information exchange. All data will reside on password-protected computers, with only the investigators and key members of the research team having access. A variety of other measures will be taken to protect confidentiality, including: We will 1) assign a unique ID number to each patient to label all components of the

protocol, instead of patient names, 2) restrict access to the key linking names and ID numbers to key staff and the PI at each site, 3) store any paper with data in a locked area. Participants will be told that agents of the IRB, and QA monitors will be allowed to inspect sections of their research records related to this study, if requested.

- Emotional Discomfort**:** The participants may experience some emotional discomfort from answering sensitive and/or personal questions. There is the possibility that the participant will feel bored.

- TOME risks*:* The education intervention has been found to be safe and efficacious in prior studies. Participants may experience embarrassment if they receive feedback about missing numerous questions about opioid-overdose and MOUD.

Benefits: The results of the present study are unlikely to have a direct substantial societal impact. However, promising results would be used in support of a larger trial to test the efficacy of TOME. The study participants 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 naloxone. Consequently, the risk/benefit ratio is favorable and conduct of the research well justified.

2. Collection and management of AEs and SAEs: In general, the risks associated with trials employing behavioral interventions are presumed minimal relative to those evaluating pharmacologic interventions. An adverse event (AE) for this trial testing a low risk, education intervention is defined as: 1. Suicidal ideation and 2. Homicidal ideation.

SAEs will only be reported for events related to an AE (e.g., hospitalization due to suicidal ideation, etc.). We will use FDA criteria for SAEs (i.e., an adverse event that results in any of the following outcomes: death, life threatening event, initial or prolonged hospitalization, disability, congenital anomaly, intervention to prevent permanent impairment or damage, or other significant medical event). The study staff will be trained to monitor for and report AEs and SAEs. Additionally, as applicable, sites will submit reporting of AEs/SAEs according to IRB requirements. Each of the sites has established practices for managing medical and psychiatric emergencies, and the study staff will continue to utilize these procedures. Treatment providers at each site will be responsible for monitoring participants for possible clinical deterioration or other problems, and for implementing appropriate courses of action.

16.7 Trial Efficacy

1. Plans for interim analysis of efficacy data: There will be no interim analysis of efficacy data by the investigators.

16.8 DSM Plan Administration

1. Responsibility for data and safety monitoring: Site study staff will be responsible for the clinical management and safety monitoring of the study participants.

2. Frequency of DSM reviews: Breaches of confidentiality will be reviewed by study leadership in regularly scheduled meetings for the duration of the study.

3. Content of DSM report: The DSM report, which will be contained in the final study report, will include a brief description of the study and any changes made. Additionally, we will report baseline sociodemographic characteristics, including age and race of the participants screened and randomized. We will also report retention rates and the disposition for all study participants. Any quality assurance issues, regulatory issues, and breaches of confidentiality will be included in the report.

16.9 DSM Board (DSMB) Plan

The MOMs (CTN-0080) trial has a NIDA CTN DSMB that is responsible for conducting periodic reviews of accumulating safety, trial performance, and outcome data. Given the low risk associated with the TOME intervention and the brevity of the study time frame, a separate DSMB was not established for the TOME trial. Instead, should Dr. Winhusen feel the need for DSMB input (e.g., as the result of an AE or SAE etc.) he will request an ad hoc meeting with the MOMs DSMB.