Study Title: Patient-Centered Care for Opioid Use Disorders in Federally Qualified Healthcare Centers and Specialty Care Settings

NCT number: Not yet available

Document Date: 6/27/17

Treatment Research Institute—Institutional Review Board

SUMMARY OF HUMAN SUBJECTS RESEARCH PROTOCOL

Please address all applicable points to create a complete and succinct synopsis of the protocol. Use language, insofar as is possible, that can be understood by an external, non-scientist layperson, and provide meanings for all acronyms used. **Form must be typewritten.**

(Maintain subheadings in body of text.)

Title of project: A Simple Large Trial of Patient-Centered Care for Opioid Use Disorders in Federally Qualified Healthcare Centers and Specialty Care Settings

Funding Source and Funding Dates (Start and End Dates):

Patient Centered Outcomes Research Institute (PCORI)
8/1/2017 – 7/31/2022 (anticipated)

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1. Introduction and rationale for study

The U.S. is combatting an epidemic of Opioid Use Disorder (OUD) that is fueled by the availability of powerful prescription opioid medications. In 2014, 10.3 million Americans reported using prescription opioids (POs) nonmedically [1]. Opioids are highly addictive and potent, resulting in a powerful withdrawal syndrome necessitating increasing amounts of opioids just to feel normal. Consequently, PO misuse can easily develop into an OUD, which, because of the cost of illicit POs, can transform into heroin dependence (which is considerably cheaper [1]), and raises the risk of overdose. Opioid overdose rates have tripled in the last 15 years, jumping from 3 deaths per 100,000 persons in 2000 to 9 deaths per 100,000 in 2014 [2]. The public health relevance of this research proposal is high.

Patients with OUD typically receive treatment in settings that are segregated from the rest of medical care. The specialty care system struggles to implement evidence-based treatments in formats that are attractive to patients, and may not meet the needs of a substantial portion of patients. Yet the need to integrate behavioral health into medical settings is widely recognized among health care professionals [3,4] and government and international organizations [5-7], as behavioral health conditions are at risk to be undiagnosed or undertreated [8,9]. However, a number of implementation issues need to be addressed: developing and testing effective ways of utilizing psychological techniques in integrated care [10,11], determining if different types of integrative models are more effective in different settings such as Federally Qualified Healthcare Centers (FQHCs) [12,13] and sustainability [14,15].

This project will determine whether a more holistic, flexible and patient-centered OUD treatment approach, Personalized Addiction-to-Health (PATH), can be implemented and sustained in existing primary care systems, and whether that approach is more effective than usual specialty care (Standard Care, SC) for OUDs on outcomes that matter to patients. A flexible, integrated primary care model for OUDs is vitally needed now, as millions of OUD patients become insured. This new model would expand access to care for patients at Federally Qualified Healthcare Centers (FQHCs) which are typically underserved in behavioral health treatments.

2. Specific aim(s)

Aim 1: To partner with funders, stakeholders, and the clinical providers of two networks of FQHCs, as well as our community and stakeholder advisory boards, to refine our collaborative care treatment protocol and health education materials.

Aim 2: To expand a sustainable reimbursement strategy to integrate evidence-based practices into FQHCs: medication assisted treatment, behavioral treatments, and recovery-oriented peer support.

Aim 3. To conduct an 18-month randomized effectiveness trial comparing a) integrated OUD treatment (PATH) to b) Standard Care (SC) to test the following hypotheses:

- Primary Hypothesis 1: Clients in the PATH condition will demonstrate higher rates of confirmed substance abstinence (hair and UA verified) during treatment and at follow-up than clients in the SC condition.
- Primary Hypothesis 2: Clients in the PATH condition will demonstrate greater retention in treatment than clients in the SC condition.
- Secondary Hypotheses: Relative to those in the SC condition, participants in the PATH condition will demonstrate:
    - Lower rates of service utilization (days of hospitalizations, emergency department visits, residential treatment)
    - Higher quality of life (Q-LES-Q-SF scores)
    - Lower rates of HIV risk behaviors (RAB total, sex, and drug risk scores)
- Exploratory Hypotheses: Relative to those in the SC condition, participants in the PATH condition will demonstrate improved Employment, Family/Social Functioning, and Psychiatric severity scores on the ASAM Criteria.

Aim 4: To demonstrate the portability and sustainability of this treatment platform in three diverse FQHC networks in two cities over an additional 12 months.

3. Endpoint(s) to be measured

Client variables that will be measured include abstinence and days of substance use; treatment engagement; quality of life; HIV risk; substance use, employment, family/social functioning, and Psychiatric severity scores; and therapeutic engagement in and satisfaction with substance abuse treatment.

4. Number of subjects to be enrolled per year and in total. These numbers should incorporate numbers screened and consented to reach enrollment.

For the process evaluation, we anticipate that we will complete semi-structured interviews with approximately 8 patients and 14 providers in Year 1. In year 2, we anticipate completing semi-structured interviews with approximately 8 different patients. We also anticipate interviewing approximately 4 new providers in year 2, along with 10-14 of the providers previously interviewed in Year 1. In year 3, we anticipate completing semi-structured interviews with approximately 8 different patients. We also anticipate interviewing approximately 4 new providers in year 3, along with 10-14 of the providers previously interviewed in Years 1 and/or 2.

In Year 1 we anticipate screening 500 individuals for a preliminary pilot study of the PATH condition. We expect approximately 12% of screening participants will meet initial eligibility criteria and consent to take part in the (about 54). Of those clients consented, we expect 36 participants will be enrolled to participate in the pilot study.

In Years 1 through 4, we anticipate screening approximately 10,000 individuals for the main study. We expect approximately 12% of screened clients will meet eligibility criteria and consent to take part in the study (about 1,200 patients). Of those clients consented, we expect approximately 800 participants will be enrolled to participate in the study (n=400 per condition).

- Year 1:We anticipate we will enroll 92 participants (36 pilot, 56 main)
- Year 2: We anticipate we will enroll 333 participants
- Year 3: We anticipate we will enroll 333 participants
- Year 4: We anticipate we will enroll 78 participants

5. Considerations of statistical power in relation to enrollment

The power analyses for Primary Hypothesis 1 were calculated following the recommendations of Liu and Wu [16]. The analysis was based on a corrected alpha of .025 (.05/2 primary outcomes), a compound symmetry covariance structure, an estimated abstinence rate of 25% in the SC condition (based on data from our prior study), a correlation between observations on the same patient of .50, and assuming 20% attrition at the final time point. We identified two primary subgroup analyses to be performed: (1) setting [recently discharged inpatients (IP, n = 400) vs. patients presenting for outpatient treatment (OP, n = 400)] and (2) type of opioid [heroin (n = 534) vs. prescription (n = 266)]. For the smallest subgroup (patients primarily using prescription opioids: n = 266; 133 per condition), we will have 80% power to detect an approximately 15% difference in abstinence rates between the conditions (i.e., 25% in control vs. 40% in experimental; OR = 2.0). This projected difference is conservative and based only on the repeatedly demonstrated, similarly scaled differences contingency management yields when compared to standard treatment conditions [17-21]. The smallest detectable differences for the remaining subgroups and the overall sample are as follows using the same specifications: (1) patients recruited from IP setting (n = 400): 12%, OR = 1.8, (2) patients recruited from OP setting (n = 400): 12%, OR = 1.8, (3) patients primarily using heroin (n = 534): 9%, OR = 1.6, and (4) the overall sample (n = 800): 8%, OR = 1.5. The power analyses for Primary Hypothesis 2 were calculated following the recommendations of Lakatos [22]. The analysis was based on a corrected alpha of .025, no attrition as chart data will be available for all patients, and estimated dropout rate of 60% in the SC condition [23]. For the smallest subgroup (patients primarily using prescription opioids: n = 266; 133 per condition), we will have 80% power to detect a hazard ratio of .59 which corresponds to a difference in survival rates of approximately 18% between the two conditions. The smallest detectable hazard ratio for the remaining subgroups and overall sample are as follows using the same specifications: (1) patients recruited from IP setting (n = 400): HR = .65, 15% difference in survival (2) patients recruited from OP setting (n = 400): HR = .65 , 15%

difference in survival (3) patients primarily using heroin (n = 534): HR = .69, 13% difference in survival , and (4) the overall sample (n = 800): HR = .74, 10% difference in survival. We have chosen to use an alpha level that corrects for the number of primary hypotheses rather than the number of subgroup analyses as the latter approach would substantially increase the likelihood of making a type 2 error [24,25].

6. Explain procedures that will involve the subject

Process Evaluation

For our ongoing process evaluation we will conduct semi-structured interviews with key clinical team members, program directors, and patients at each of the health center sites. These interviews will take place at three time points – first in Year 1 prior to the randomized trial, once in Year 2, and again in Year 3 in order to obtain implementation feedback throughout the project. Participation in these semi-structured interviews will be voluntary, and all participants will complete informed consent as outlined in Item 9 below.

Providers. We will interview approximately 14 providers and program directors at each time point. Provider participants will not receive payment for their participation. Provider participants will be asked about their opinions on integrating substance use treatment into primary care, medication assisted treatment, contingency management, and barriers to implementation.

Patients. Eight patients, 2 from each site, will be asked to complete interviews at each time point. Interviewees in Year 1 will be participants from the Pilot Phase who received the PATH intervention. Interviewees in Years 2 and 3 will be participants who complete the PATH or SC protocol. Participants will be asked about the acceptability of the intervention they received, and asked for recommendations on how to improve the intervention. For the Year 1 interviews, we will ask the first 2 patients from each site that complete the intensive intervention phase to participate in this interview. Should any participant decline, we will ask the next participant who completes the intensive intervention phase of PATH. For the Year 2 and 3 interviews, we will designate a "start date," and beginning on that date we will ask the first PATH and SC patient from each site who complete the 12-month follow-up assessment to participate in the interview. As with Year 1 interviews, should any participant decline, we will ask the next participant from that condition who completes the 12-month follow-up. Participants who agree to be interviewed will complete a separate informed consent for this portion of the study, as outlined in Item 9 below. Patient participants will be paid $50 for their time and travel to the interviews.

All semi-structured interviews will be audio recorded, and the recordings will be transcribed; transcripts will be stripped of identifying information, and the audio recordings will be destroyed to protect confidentiality.

Research Trial

Research participants will be individuals with moderate to severe OUD who are new or existing patients in outpatient Federally Qualified Health Centers (FQHCs). FQHCs are primary care centers that serve an underserved area or population and provide comprehensive services, including preventive health services, dental services and behavioral health services. Integrated behavioral health is typically provided by a Behavioral Health Consultants (BHCs), Licensed Clinical Social Workers who provide brief interventions and referral services for a range of behavioral and psychiatric issues. For this study, each FQHC will designate a team of care providers to administer the study interventions, including a BHC, a Peer Recovery Specialist (PRS), a Psychiatric Nurse Practitioner, and an Addictions Psychiatrist.

Recruitment procedures, including screening and informed consent, are described below in Item 9. As part of their treatment experience, all patients who provide informed consent will continue to receive all other standard primary care medical treatment.

Patients who provide informed consent will complete the ASAM Criteria Software interview with a research assistant. Final eligibility will be assessed based on the ASAM Level of Care.

> Participants will be eligible if: 1) they are 18 years or older, 2a) they meet the criteria for Level 1 care, i.e., outpatient treatment, as defined by the ASAM Criteria, and determined for the patient's needs according to the decision engine built into the ASAM Criteria Software, or 2b) they meet criteria for Level 2 care (Level 2.0), i.e., intensive outpatient program..
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> Patients will be ineligible if: 1) the medical practitioner or BHC overrule these criteria because medical and psychiatric complications exist that would contraindicate research participation; 2) they have an ASAM level of care higher than 2.0, 2) they report plans to leave the area (i.e. Philadelphia or Washington DC greater metropolitan area) within the next 6 months; (d) they ae not English-speaking; or 3) they are unable to provide valid informed consent by correctly describing the key components of consent to the RA.

Patients who require the highest level of care and are on Levels 3 and 4 of the spectrum, i.e., inpatient or residential care, will be ineligible and will be referred immediately for appropriate treatment.

Client Baseline Procedures

Following the ASAM, eligible patients who agree to participate will complete a comprehensive Locator Form a Research Assistant (RA) that provides research staff with numerous contact numbers to assist in locating participants at set follow-up points. The RA will then complete the remaining baseline assessment measures (listed below in item 7) including collecting a hair and urine sample. Research staff will also verify the information provided on the Locator Form by contacting the telephone numbers (including those of collaterals) provided on the Locator Form.

Pilot Study: Participants enrolled in the pilot study will be assigned to receive the PATH intervention as described below. Pilot study participants will be asked to complete the following follow-up assessments: a weekly Substance Use Inventory during weeks 1 through 6, and then comprehensive follow-ups at 3 and 6 months post baseline. Assessment instruments are described below in Item 7. Pilot Study participants will be paid $10 for completing weekly assessments and $50 each for the 3 and 6 month follow-ups.

Main Study: Patients enrolled in the main study will be randomly assigned to one of two conditions: PATH or SC. Random assignment will be stratified by 1) whether they are a new or existing patient at the FQHC, and 2) the FQHC site where they are enrolled.

Intervention Procedures

Patients in either condition with severe SUDs with serious withdrawal complications may require detoxification, and possibly a residential stay. If we encounter more severe patients during the recruitment period, they will be referred for an inpatient stay, and allowed to present for enrollment in the study following discharge from their inpatient stay.

Standard Care

Patients randomly assigned to Standard Care will be referred to treatment at a publicly funded IOP program with MAT capability for OUD. In order to complete this referral, a BHC or PRS will meet with the patient for up to 4 brief sessions.

Participating IOPs offer dual diagnosis treatment and psychiatric medication management, and various services in case management, psychoeducation groups, and vocational rehabilitation. Each program has an MAT induction protocol that is offered in greater intensity in the first weeks of treatment; once a patient is stabilized and demonstrating abstinence, they can then attend fewer medication management visits. IOP programming consists of nine hours of group (typically delivered in three three-hour blocks) and one hour of individual. All of these programs strive to integrate ESTs and 12-Step as a cornerstone to their approach. IOPs typically last 3-4 months, and then step down to outpatient management, which is typically 3 hours per week for up to 9 months, and as needed after that. Patients assigned to SC will still receive primary care at the FQHC.

PATH

Patients randomized to PATH will receive their OUD treatment in the FQHC on a flexible, individualized schedule. The PATH care team – a BHC, a Peer Recovery Specialist (PRS), a Psychiatric Nurse Practitioner, and an Addictions Psychiatrist – will provide patients with an evaluation/individualized treatment plan based on the standardized needs assessment from the ASAM Criteria interview and the SAMHSA Recovery Support Services Questionnaire. The treatment plan will focus on reduction of opioid use, psychiatric stabilization, pursuit of the patient's individual recovery goals and meeting support service needs. The course of treatment is scheduled for 1 year, with medication induction occurring in Weeks 1-4, and then transitioning to maintenance in ensuing weeks. Behavioral Treatment is most intensive in Weeks 1-13 (twice weekly), dropping to weekly for Weeks 14-26, and then as needed in Weeks 27-52. Treatment components include:

1. Medication Assisted Treatment (MAT): The medical providers will offer MAT for addiction: primarily injectable extended-release naltrexone (XR-NTX) [26,27] and office-based buprenorphine (agonist treatment) [28]. Patients will initiate these treatments in our primary care settings, in some cases participating in an ambulatory detoxification / induction on site **(OP patients)**, or being inducted after an inpatient detoxification **(IP patients)**. Providers will also be trained and supervised to be able to diagnose, determine treatment recommendations, initiate, and maintain outpatient psychiatric treatment per the highest tier of these specifications of the ASAM Criteria. The personalized aspect of PATH emphasizes some patient choice, with the option to pivot from one medication to another based on patient response and preference. The flexible protocol will allow opioid dependent patients to: a) remain on or taper off a long-term agonist (buprenorphine); or b) convert to antagonist (XR-NTX).

Buprenorphine. Induction from illicit opioids onto buprenorphine will be managed by a formal protocol, developed by the federal government and which is available at: http://www.ncbi.nlm.nih.gov/books/NBK64245/pdf/TOC.pdf. Forms for patient and supportive significant other treatment agreements and tracking/log/patient count forms are also available online at: http://pcssmat.org/opioid-resources/clinical-tools/#1382013035-2-36. Drug storage and security will be managed locally at each FQHC by the facility's pharmacy. For patients who wish to stop their buprenorphine treatment, the protocol will be used to plan patients' gradual tapers when the patient decides to conclude maintenance therapy. Tapering patients will be offered the option of an agonist-to-antagonist transition, as current clinical thinking holds that this may ameliorate an otherwise significant rate of termination withdrawal relapse [29].

Vivitrol (XR-NTX). Patients who elect Vivitrol will first receive detoxification, as Vivitrol administration can precipitate withdrawal if given to a person who is physiologically dependent on opioids. Patients will be checked for dependence by conducting a history of recent drug use (utilizing the ASAM Criteria Software), examining the patient for fresh puncture marks and signs or symptoms of withdrawal, taking a urine drug screen, and when uncertain, conducting a naloxone challenge test. The naloxone challenge provides a good antagonist challenge that, if positive, provokes only the briefest episode of withdrawal symptoms and allows the patient to then undergo proper detoxification prior to the first Vivitrol injection. Detoxification and induction onto Vivitrol will utilize recommended protocols that have been implemented on an outpatient basis with good retention and follow-through by patients [29,30]. Detoxification will occur…

Once detoxification is established, patients will be administered the first dose of Vivitrol. Plasma concentrations of naltrexone and 6-beta naltrexol (its main metabolite) are detectable for at least 30 days after a single injection, and the medication must be re-administered to maintain its effect. Repeat doses will be scheduled 30 days (±7 days) after the last dose, and if the patient is beyond this period, re-evaluation using the protocol above will be performed for the possibility of re-establishment of physical dependence.

Medication Support. Patients receiving either medication will be given initial and ongoing support to increase understanding of the role of medicine (e.g., foundational and stabilizing, but requiring psychosocial treatment), the medication options, and differences in side effects and risks. Periodic re-evaluation will examine with the patient his/her progress towards goals and, in the event of less than anticipated progress, review the contingency plan (e.g., medication or dose changes, co-occurring disorder management, and escalation of recovery support).

2. Cognitive-Behavioral / Relapse Prevention with Contingency Management: The BHC will deliver manualized cognitive-behavioral relapse prevention (CB/RP) along with contingency management (CM). During Weeks 1-13, patients in the PATH condition will come to the FQHC twice per week for CM and CB/RP sessions. CB/RP will then continue with once weekly sessions in Weeks 14-26, and as needed but tapering in frequency for Weeks 27-52. Procedures for CM and CB/RP are as follows:

Urine Sample Collection and Testing. Patients will be scheduled to provide urine samples twice weekly prior to seeing the LCSW for their regular counseling visits, which will be separated by 2 or 3 days. Samples will be collected under direct observation by a same-sex staff member. Valid samples will be tested for Opioids using quick read test strips at the cutoff levels established by SAMHSA to indicate substance abstinence (specific testing materials to be determined by the FQHC's billing and reimbursement practices). Urinalysis results will be entered into a database that calculates the value of the voucher to be delivered.

Abstinence-based Voucher Reinforcement Schedule. Upon delivery of the first drug-negative urine sample, patients will receive a $2.50 voucher. The value of the voucher will increase by $1.50 with each consecutive negative sample. A $10 bonus voucher will be given after each delivery of 2 consecutive negative samples. A $50 bonus voucher will be given if all 26 samples are negative. The maximum earnings per patient is $732.50 If a sample tests positive, patients will not receive a voucher on that day, and the voucher value will be reset to $2.50 for the next negative sample provided. The voucher value will also reset if a patient fails to provide a scheduled sample. Patients can avoid being reset by arranging excused absences in advance for vacations, funerals, or other valid reasons and providing verification at their next visit (e.g., hotel receipts, funeral program). Whenever possible, appointments will be scheduled so that two samples can be provided every week. When 3 consecutive negative samples are provided following a reset, the voucher values will be restored to the highest amount earned prior to the reset. This procedure prevents patients from becoming discouraged and giving up and rewards them for getting back on track quickly. Patients can immediately exchange their vouchers for gift cards to a wide variety of stores or can bank their earnings to save for a special purchase. The BHC will discuss

exchanges with patients, encouraging them to select recovery-oriented purchases (for example, movie tickets, gym memberships, clothing for interviews).

CB/RP Counseling Sessions. CB/RP sessions are 30-40 minutes in length and dovetail with the CM voucher system. The BHC will help patients plan to avoid high risk situations and deploy learned coping skills to make it from visit to visit without using. The BHC also will help the patient address other lifestyle issues, conduct conjoint sessions with family members or significant others, and will explore risk for contracting HIV and determine whether the patient has been tested. Voucher accumulations are celebrated, and plans for how the patient will use the earnings (movies, shopping vs. groceries, bills) are discussed. Over time, the emphasis shifts from the vouchers to the fact that the patient has now accumulated abstinent time, giving the medications time to work and facilitating the patient's adaptation to a recovery lifestyle.

3. Recovery Support Services: Peer Recovery Specialists will work with the BHC to aid the patient in social service needs, help patients stay motivated and connected and begin focusing on personal recovery goals. Patients will set goals with the Peer Specialist and professional SUD treatment team to improve housing and employment, family / social functioning, manage child care, develop supportive relationships and establish a daily routine. The Peer Recovery Specialist will help the patient access community resources, and offer longitudinal peer / relational support. The Peer Recovery Specialist also provides a model of a recovery lifestyle. If a patient goes missing, the Peer Specialist will seek out the patient by telephone or through contacts and re-engage them.

Follow-up Procedures

We will complete follow-up assessment interviews with participants at 3-, 6-, 9-, 12-, 15- and 18-months post-baseline. Follow-up assessments will take place in-person, generally at the FQHC site. If the participant is not able to travel to the FQHC (or they have been discharged and are not allowed back on the premises), then we will meet them in a safe, neutral location such as a restaurant or public library. The assessment battery will be similar to that collected at Baseline (see Item #7), and we will collect a hair and urine sample. If a participant is incarcerated at any follow-up point research staff will not attempt to contact the participant while incarcerated.

We will also call participants every month that a follow-up assessment is not due (i.e. months 1, 2, 4, 5, 7, 8, 10, 11, 13, 14, 16, and 17) to verify the Locator information they provided at baseline, and update any information that has changed.

We will use patient-provided information on the Locator form to contact participants. Research staff will use participant tracking software to ensure that they are alerted when call windows open at each assessment point. Research staff will call participants at the times and numbers indicated on their Locator Form as the best time to reach them. For participants who are more difficult to reach, call times and call numbers will be alternated. Participants will be mailed reminder notices informing them of an upcoming interview, as well as thank you notes for completing interviews. Research staff will attempt to contact participants via any other mechanisms that the participant consented to on the Locator Form (e.g. email, Facebook, home address). For participants who are unreachable, messages will be left at all contacts that the participant consented to on the Locator Form, and postcards will be sent to contacts that we cannot reach on the phone. Should contact persons indicate that they have lost track of the participant, research staff will search for the client using available public search mechanisms (www.whitepages.com, etc.). When participants are reached by telephone, research staff will schedule the date and time of the interview and will update the Locator Form if the client's contact information has changed. In addition to contacting clients to schedule assessments.

Confidentiality. We have devised IRB-approved procedures to safeguard client confidentiality while attempting to locate them. RAs will call participants from either a study provided cell phones or from TRI's office phones. TRI's calling system blocks the name "Treatment Research Institute" off of its

listing, preventing the incoming phone from accessing TRI's name. If a participant registers more significant confidentiality concerns, research staff will call from blocked cell phone numbers that do not display the return number. When messages are left for the participant on recording devices or with collaterals, research staff members report that they are trying to reach the participant to complete a "health care survey" that the participant volunteered for. Additional protections for client follow-up can be found in item 11.

Participant Payments

Main research trial participants will be compensated $50 for completing each research assessment (Baseline, 3-, 6-, 9-, 12-, 15-, and 18 month follow-ups). Main trial participants will also be compensated $5 each month they do not have a scheduled follow-up assessment and they provide research staff with their contact information (Months 1, 2, 4, 5, 7, 8, 10, 11, 13, 14, 16, and 17). In total, participants will be compensated $410 for completing all study activities. All payments will be in the form of gift cards.

7. Identify the sources of research material obtained from individually identifiable living human subjects in the form of specimens, records, or data.

Measures that are part of the patients' medical record

We will obtain consent from patients to use the clinical data listed below for research. These measures may be part of patients' medical records, and can be linked back to the patient.

Screening Only:

CO-Triage: CONTINUUM™ Triage (CO-Triage™) [31] is a provisional triage tool for alcohol and substance problems, and identifies broad categories of treatment need along the six ASAM Criteria Dimensions. The decision logic in CO-Triage calculates the provisionally recommended ASAM Level of Care which will provide screening cut-offs for pre-eligibility.

Screening and Follow-up (administered at Screening and all Follow-ups):

ASAM Criteria Software: The ASAM Criteria conducts level-of-care matching [32], i.e., to hospital *vs.* residential *vs*. intensive outpatient *vs.* outpatient care settings. This structured interview assesses objective and patient self-report data to produce multi-dimensional problem severity ratings (medical, employment, self-reported alcohol and drug use, family/social, legal, and psychiatric), used to recommend optimal patient outcome at the least restrictive setting or level of care [33,34]. The software yields a standardized recommended level-of-care [35] with good inter-rater reliability [36] and convergent validity [37], as well as a full DSM-IV and DSM-V SUD diagnoses with symptom/criteria counts. Patient-care matching on the ASAM Criteria scales demonstrate predictive validity on client outcomes [38-41]. This instrument is roughly 1100 items and exists as an online assessment tool. Please accept the following link to access information regarding this tool: http://asamcontinuum.org/

Measures collected for research purposes only

The measures listed below are collected for research purposes only and will not become part of patients' medical records. These measures will be stored separately from those collected as part of the medical record, and only TRI researchers will be able to link this data to the patient.

Weekly during Weeks 1 through 6, Pilot Study Only:

Weekly Timeline Followback (TLFB): The TLFB [42] is a structured interview which helps patients recall their substance use to reflect a specified period. Patients are presented with a calendar representing the past 7 days, and the interviewer helps the patient anchor the calendar with memorable events to reconstruct their use (dates, amounts) over the designated period.

Baseline and Follow-up Instruments (administered at Baseline, 3-, 6-, 9-, 12-, 15-, and 18 month follow-ups):

Urine testing: On-site urine drug testing kits (ACON International) rapidly (5-minute) test for cocaine, opiates, amphetamines, methamphetamines, benzodiazepines, cannabis, barbiturates, PCP, and alcohol. Urine testing will be administered at all follow-ups to capture very recent use (i.e. past 3 days).
Hair follicle testing: Hair follicle samples will be sent to an accredited laboratory for testing. Samples generally provide a 90-day window of use, and will be tested for opiates, cocaine, amphetamines, methamphetamines, ecstasy, marijuana, and PCP. If a hair sample of 1.5 inches cannot be provided, urine sampling only will be performed.
Non-Study Medical and Other Services (NSMOS): This questionnaire was adapted from the Treatment Services Review [43,44] for patients in medical settings. The NSMOS counts substance abuse treatment, medical services, visits to medical offices, hospitalizations, and emergency room visits received that were not a part of the assigned treatment.
FQHC / SUD Treatment Program Case Review: Chart review will verify patient self-report of treatment engagement. We will obtain the first version of this data by pulling payment data from funders. We will resolve inconsistencies between patient report and billing data through chart review.
Texas Christian University Treatment Engagement (TCU ENGForm): The TCU ENGForm [45] measures patient therapeutic engagement in and satisfaction with substance abuse treatment. It includes 36 items from four scales representing Treatment Participation, Treatment Satisfaction, Counseling Rapport, and Peer Support, and it takes approximately 10 minutes to complete.
Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form. The Q-LES-Q-SF [46] is a 16-item self-report measure designed to measure participant enjoyment and satisfaction experienced in various areas of daily functioning.
Risk Assessment Battery (RAB): This 38-item self-report measures past 3-month drug use, injection-related risk behavior, sexual risk, and HIV testing history and results. The RAB shows excellent reliability, and discriminant and predictive validity for seroconversion amongst drug users [47,48].
Chart Review: By prior patient consent, the health centers and SC substance abuse treatment programs will release study patient records for the following information: treatment session attendance, medications prescribed, prescriptions filled, doses received, and results from urinalysis testing.

8. Describe characteristics of the subject population, such as their anticipated number, age ranges, sex, ethnic background, and health status. The study should employ a study design with gender and race representation appropriate to the purpose of the research. Strong justification must be provided for exclusion of broad population groups. Identify the criteria for inclusion or exclusion. Explain the rationale for the use of vulnerable populations as research subjects (i.e., prisoners, pregnant women, disabled persons, drug users, children).

Research participants will be individuals with moderate to severe OUD who are new or existing patients in outpatient primary care settings. Patients will be eligible if: 1) they meet the criteria for Level 1 care, i.e., outpatient treatment, as defined by the ASAM Criteria, and determined for the patient's needs according to the decision engine built into the ASAM Criteria Software, or 2) they meet criteria for Level 2 care (Level 2.0), i.e., intensive outpatient program. Patients will be ineligible if: 1) they have an ASAM

level of care higher than 2.0, 2) if they are under 18 years of age, or 3) they are unable to provide informed consent.

We anticipate that the demographic characteristics associated with the patients will be similar to the characteristics of the patients enrolled in the participating FQHCs. These patients are, on average, 60% female, 68% Black, 10% White, 22% other minorities or more than one race, and 12% Hispanic.

We will not exclude any potential counselor or client participants based on race or gender. Members of gender and minority groups, the elderly, and disabled will be included in the research in the same proportion as they are represented in the populations of the recruited substance abuse treatment programs. Participants with disabilities will be accommodated. We will continuously monitor gender and racial minority representation in the sample to ensure that it is representative of the target population. In the unlikely event that it becomes necessary, we will over-sample gender and racial groups that are significantly under-represented relative to their prevalence in the target population.

9. Describe plans for recruitment of subjects, including advertisement and posters and the consent procedures to be followed, including the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects and the methods of documenting consent.

Patients will be recruited for this study via several avenues:

FQHC Patient Identification. Participating FQHC sites will institute a standard screening protocol. Site staff will screen all patients presenting for an appointment on a yearly basis using the CO-Triage. All patients that meeting criteria using this measure will be referred to the BHC and RA for further assessment (see below).

IP Patient Identification: Study staff will connect with and cultivate relationships with intake facilities, detoxification, inpatient and residential facilities, and outreach programs to inform case workers and clinical staff about the study and treatment options being offered to encourage referrals for patients who are either not in treatment for SUD or are in treatment in a short-term inpatient setting but do not have outpatient discharge plans. We will accept referrals for patients not currently engaged in primary care, or for those willing to switch their primary care provider. Patients in IP settings will be screened prior to discharge by an RA using the CO-Triage. Those that pre-qualify will be referred to a participating FQHC upon their discharge for further assessment (see below).

IOP/OP Patient Identification: Study staff will connect with and cultivate relationships with outpatient treatment programs to inform case workers and clinical staff about the study and treatment options being offered to encourage referrals for patients who are presenting for treatment. We will accept referrals for patients not currently engaged in primary care, or for those willing to change primary care providers. Patients referred from OP settings will be screened by an RA using the CO-Triage. Those that pre-qualify will be referred to a participating FQHC upon their discharge for further assessment (see below).

Advertising. We will also recruit through advertisements (e.g., radio, newspaper, billboards, yellow pages listings, informational brochures). All advertisements will include a study hotline that will be directed to a study RA. Callers will be screened using the CO-Triage, and those that are not currently engaged in primary care, or are willing to change primary care providers will be referred to a participating FQHC upon their discharge for further assessment (see below). All advertisements will be approved by the IRB.

Screening

Research assistants (RAs), BHCs, and other FQHC staff will screen patients offsite and in the host FQHCs using the CO-Triage as described above. Patients who meet screening criteria for Level 1 or 2 care on the CO-Triage will be invited to complete the ASAM Criteria Software interview to determine if they meet study criteria.

Patients who are identified as potential study participants through the processes described above will be asked to complete a screening consent with an RA. We are requesting a waiver of written documentation of consent for the screening process. According to 45 CFR 46.117(c), written documentation may be waived if "the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from breach of confidentiality." The screening consent form would be the only written document linking the patient to the research, thus a requirement for written consent would paradoxically be the only real danger to loss of privacy and confidentiality for participants who agree to be screened. We will provide an information sheet to patients prior to screening that contains informed consent information, and we will obtain verbal consent that the patient is willing to participate in the screening.

For patients who consent to screening, an RA or BHC will administer the ASAM Criteria Software interview to determine if they meet DSM-V criteria for a Moderate to Severe OUD diagnosis with ≥4 symptoms and opioid use within the past month. Patients meeting criteria must also affirm that they are not currently engaged in primary care (no provider, or no PC contact in the past year), and be willing to receive care at the participating FQHC. Eligible patients will then be invited to complete informed consent with an RA.

Inclusion and Exclusion Criteria

Inclusion Criteria: 1) patient is 18 years or older, 2a) they meet the criteria for Level 1 care, i.e., outpatient treatment, as defined by the ASAM Criteria, and determined for the patient's needs according to the decision engine built into the ASAM Criteria Software, or 2b) they meet criteria for Level 2 care (Level 2.0), i.e., intensive outpatient program..

Exclusion Criteria: (a) the medical practitioner or BHC overrule these criteria because medical and psychiatric complications exist that would contraindicate research participation; (b) they have an ASAM level of care higher than 2.0, (c) the patient reports plans to leave the area (i.e. Philadelphia or Washington DC greater metropolitan area) within the next 6 months; (d) the patient is not English-speaking; (e) if the patient is unable to provide valid informed consent by correctly describing the key components of consent to the RA.

Informed Consent

During the informed consent process, patients will be fully informed of the procedures, the nature of the study conditions, the randomization procedure, inclusion and exclusion criteria for the study, and the compensation associated with participating in the study. They will be informed which research data may be part of their medical record (as specified above in item 7), and which research data collected in the study will be kept strictly confidential. The only exceptions to confidentiality (clearly specified in the consent forms) will pertain to information related to medical emergencies, disclosure of current child/elder/dependent abuse or neglect, or imminent risk of death or serious injury to the participant or others. Potential participants will also be informed of all known potential risks and benefits of participation, their right to refuse or revoke consent at any time, and the names and phone numbers of individuals they may contact for additional information or to register complaints about study procedures. They will also be asked to complete a brief consent quiz to ensure their understanding of the study requirements, the risks and benefits, and their human subject protections. All items answered incorrectly will be reviewed until the potential participant demonstrates at least a 95% understanding of the essential elements of the informed consent document. Potential participants will then be asked if they have any questions and will be asked to sign the informed consent form to document their agreement to participate. They will receive a duplicate copy of the consent form for their records. The original signed consent form will be kept in a locked filing cabinet only accessible to research staff.

10. Discuss whether risks to the subject are 'minimal' or 'greater than minimal.' List the major risks of subject participation. Describe any possible benefits of subject participation. Are the risks to subjects reasonable in relation to the anticipated benefits to subjects and in relation to the importance of the knowledge that may reasonably be expected to result?

There are six anticipated potential risks associated for participants enrolled in this study. The procedures for minimizing these risks are detailed below in item 11.

1. Perception of coercion: It is possible that some participants may feel coerced to participate in the research study. Our previous studies with similar populations indicate that this is a rare event.
2. Discomfort answering research questions and/or providing biological data: Participants may experience mild and transitory psychological discomfort from completing research measures that deal with emotionally laden material or from providing urine or hair samples. The probability of these risks and the magnitude of the anticipated harm are likely to be small. These events have *not* been encountered in any of our previous studies using similar assessments.
3. Discomfort associated with the treatment intervention: Participants may experience emotional distress given that the interventions are designed to encourage them to become more aware of their own substance use behaviors and how those behaviors may be impacting their physical and psychological wellbeing. We expect this level of distress to be similar to that which patients would experience during any psychological or psychoeducational intervention, and thus is not a function of research participation per se. We have not encountered any instances of significant emotional upset with individuals who have participated in our previous investigations of psychosocial interventions.
4. Possible side effects from medication assisted treatment (MAT): As part of this study, participants in the PATH condition will be offered access to MAT as part of their suite of treatment options. No participant will be forced to engage in MAT; the decision about whether MAT is appropriate will be made by the participant and their medical provider. However, if a patient is in the PATH condition, the patient and provider decide that MAT is appropriate, and the patient is inducted onto medication, then the patient may be at risk for possible side effects from the MAT. Importantly, our intervention is making only FDA approved medications available for appropriate indications.
5. Harm from breach of confidentiality: Participants are at risk for harm as a result of being identified as a study participant or as someone with an opioid use problem. The likelihood of this occurring is small.
6. Discomfort associated with allowing semi-structured interviews to be audio recorded (*for process evaluation only*): Patients who participate in the interviews for the process evaluation may experience mild and transitory psychological discomfort when their interviews are being audio-recorded. The probability of these risks and the magnitude of the anticipated harm are likely to be small.

Benefits to Participants: Participants may benefit from receiving an intervention (either SC or PATH) which is designed to help patients achieve abstinence or reduction in opioid use and retention in treatment.

Importance of Knowledge to be Gained: The aim of this project is to test the impact of a PATH approach to assist opioid-dependent patients in reducing substance use and improving related outcomes. If PATH proves to be effective, patients will demonstrate detectable reductions in substance use and higher engagement rates with OUD treatment during the 18-month follow up period. We will also measure other outcomes of great importance to stakeholders, patients, and their families such as medical functioning, employment, and quality of life outcomes.

11. Describe the procedures for protecting against or minimizing any potential risks, including physical, psychological, legal and confidentiality risks, and assess their likely effectiveness. Where appropriate, discuss provisions for insuring necessary medical or professional intervention in the event of adverse events to the subjects and for monitoring the data collected to insure the safety of subjects. Also, where appropriate, describe alternative treatment and procedures that might be advantageous to the subjects.

1. Perception of coercion: The RAs will be trained to describe the study to eligible patients, including the risks and benefits, prior to offering an invitation to participate in the study. The RA will clearly state that the patient's decision to participate is voluntary and that it will not impact the services they would otherwise receive at the health center. In addition, patients will be told that health center staff have no vested interest in their participation and will receive no benefit if they choose to participate. All potential participants will be told that if they feel any pressure to participate from anyone they can voice this concern to the FQHC staff, the PI, or other TRI research staff, and the PI will discuss this matter with the health center director and/or other appropriate individuals.
2. Discomfort answering research questions and/or providing biological data: Individuals in any study may experience mild and transitory emotional discomfort when answering the questions posed in interviews and on questionnaires, or providing a urine or hair sample. All participants will be informed about these possible risks before signing the consent form. Urine samples collected for research purposes only will not be collected under observation. Samples collected from PATH patients for contingency management will be collected under observation by health center medical assistants. Urine collection staff and research staff will complete a training regarding monitoring and addressing emotional distress among research participants, and a training on the urine and hair collection process which will include suggestions for decreasing participant discomfort. Participants will be told that they can choose not to respond to a question that they find upsetting and can withdraw from participation at any time without negative consequence.
3. Discomfort associated with the treatment interventions: Participants may experience mild and transitory psychological discomfort while participating in the treatment interventions. Dr. Brooks (Co-I) and the Clinical Supervisor will jointly train the BHCs to monitor patient participants for distress by observing their behavior during their assessment and intervention sessions. This training will focus specifically on helping patients to manage difficult feelings, screening them for potential harm to self and others, and implementing methods to help ensure their physical safety and emotional well-being. If necessary, the BHCs can obtain timely clinical consultation about the participant's distress by contacting the Clinical Supervisor.
4. Possible side effects from MAT: If the patient and his/her provider decide that MAT is appropriate, and the patient is inducted onto medication, then the patient may be at risk for side effects from the MAT. To minimize this risk, the providers trained to deliver MAT in this study will be fully trained on how to appropriately and safely prescribe MAT. Providers will also be trained to thoroughly advise patients about the possible known side effects associated with each medication. Our team will also monitor for frequency of expected and unexpected side effects, intervene when appropriate, and will report side effects of unusual manifestation or unusual frequency to the IRB and DSMB.
5. Harm from breach of confidentiality: Identifiable data collected for study purposes only will be kept strictly confidential and will not be shared with anyone outside of the research team. Data collected as a part of the patients' medical records will also be kept confidential per site HIPAA regulations. The only exceptions to confidentiality (clearly specified in the consent form) will be for information related to medical emergencies, child abuse or neglect, or imminent risk of death or serious injury to the participant or others. All research specific materials will be coded with a research number to de-identify the data and will contain no other identifying information. Information collected on paper (e.g., consents) will be stored in locked filing cabinets at TRI or the participating health centers. Computer spreadsheets will be saved in password-protected files. Participants will be assigned an

identification number which will be affixed to all collected data. Linkage between participant identity and identification numbers will be stored in a password protected electronic file available only to designated research staff. All research instruments will be computerized for this study, and the data will be entered via the Web into the secure ASAM Criteria system and a secure server located at the University of Pennsylvania's Data Management Unit. Efforts to contact participants for follow-ups will make no mention of the study until it is established that the participant has been reached. Access to participants' contact information will be limited only to research staff members who need to contact a participant for study purposes. Should any breaches of confidentiality occur, they will be reported to the relevant IRB, DSMB, and PCORI officials.

6. Discomfort associated with recorded interviews (*for process evaluation only*): This risk applies only to patients who agree to participate in the semi-structured interviews for the process evaluation. This level of distress is likely to be similar to other situations when people are audio-recorded or videotaped for any purpose. Usually, if any discomfort is experienced, it is very temporary. Participants will be reminded during the informed consent process that their responses are confidential and will be de-identified, and that their interviews will not be shared with anyone other than appropriate research personnel, and will be erased within five years after the completion of the study. During informed consent, participants can choose to have their interview responses typed up by research staff if they do not wish to be audio-recorded; participants who agree to be recorded can ask to stop the recording at any time. Digital audio recordings of process evaluation interviews will be coded/saved with the date of the session and an interview code; no personal identifying information will be placed in the filename or intentionally dictated into the audiotape. Research staff who are responsible for transcribing the content will also be responsible for erasing identifying information from the audiotape and ensuring that identifying information does not appear in the transcript. All digital audio files will be destroyed no later than 5 years after completion of the study.

12. Describe procedures for reporting Serious Adverse Events (SAEs) and Adverse Events (AEs), and Unanticipated Problems. Include the definition of SAEs and AEs.

Serious Adverse Events (SAEs) will be defined as 1) death or 2) a life threatening event such as suicide attempt or inpatient hospitalization due to psychiatric distress, drug/alcohol overdose, or severe reaction to a prescribed medication. A component of the study interventions involves referral to specialty treatment, including inpatient hospital-based treatment as appropriate. Admission to hospital-based inpatient substance use treatment will not be defined as an SAE unless, as noted above, it occurs as a result of or in conjunction with clinical worsening, overdose, or complications due to alcohol/drug use. Childbirth, pre-planned elective procedures, and unrelated medical events that require hospitalization will not be considered SAEs. Participants in this study are substance dependent and are thus at risk for clinical worsening. Although we do not believe the study procedures or intervention places participants at increased risk for clinical worsening, we will review and report events of clinical worsening that leads to hospitalization. These events are not anticipated to occur on a regular basis.

Adverse Events (AEs) will be defined as report of coercion to participate in the study; significant discomfort from answering research questions or providing urine/hair samples such that the participant decides to stop their participation; significant discomfort or distress from participating in the intervention; significant discomfort or distress from having process interviews audio-taped; negative side effects due to breach of confidentiality; significant increase in drug/alcohol use or psychiatric symptoms compared to baseline; suicidal ideation; or adverse reactions to MAT. For patients on MAT, we will consider any reaction to the medication that is not a known side effect to be an AE. We will also consider any severe reaction to a medication to be an AE, even if the reaction is a known side effect. We will monitor attrition rates, but drop out from the study will not be reported as an AE. Clinically insignificant

events (e.g., cold/flu, common headache) are not considered AEs. Participants may have medical and psychiatric problems which may continue during the course of the study. As per the definition of AEs, only significant worsening of baseline medical and psychiatric status or new problems will be reported as AEs. The AEs listed above have been known to occur in prior research with substance dependent populations. However, due to the protections put in place we do not anticipate reports of coercion to participate; significant discomfort from answering research questions, providing urine/hair samples, participating in the intervention, or recorded interviews; or side effects due to breach of confidentiality. Substance abuse and psychiatric disorders are often chronic relapsing diseases, and therefore we anticipate a small percentage of clients will report an increase in drug/alcohol use or psychiatric symptoms during their participation in the study. However, as stated above we will only report these if they are a significant increase from baseline.

All adverse and serious adverse events occurring during the study are documented on a form, reviewed and signed by the Co-PIs or Co-I and reported to TRI and other applicable IRBs. All SAEs are reported to the IRBs within 48 hours of our awareness of the event (24 hours for fatal events). A summary of all SAEs and AEs that occurred during the previous year will be included on the annual progress report to the relevant IRBs.

13. If this study is a chart review, indicate the time frame of data to be collected (from when to when). Also, will the data be collected anonymously (meaning that only aggregate data will be collected, and there will be no names or codes maintained to match the data with the original files)?

We will collect data from participants' charts at the health centers and substance use treatment centers as part of this study. This information will include the client's name, discharge status, individual and group counseling attendance, prescribed medications and dosage, and results of urine drug tests at the treatment center. We will collect this information beginning on the participant's study enrollment date and ending on the date the client completed involvement in the study. The data will not be collected anonymously, as we will need to link the chart data to specific participants in order to determine study outcomes. However, we will de-identify all research data collected from the charts; this data will be linked and stored under the participants' research identification numbers. All chart data will be provided to TRI by the participating health and treatment centers.

14. Children, defined as individuals under the age of 21, must be considered for potential enrollment in every study as subjects unless there are scientific or ethical reasons for excluding them. See below for the permissible exclusionary circumstances listed in the NIH Policy. If no exclusion applies: 1) discuss your plan for the inclusion of children; 2) justify the age range of children to be enrolled; 3) indicate the expertise of the research team with regard to children; 4) describe the facilities for the children; 5) indicate the number of children to be enrolled to give sufficient power for meaningful analysis; 6) describe how the assent process for children 7 to 18 years of age will be carried out.

Justify your exclusion based on one of the exclusionary circumstances listed:

- The research topic is irrelevant for children
- Children are barred by law from participation because of the risk
- Study is redundant; knowledge is being obtained in another study or is already available
- Separate age-specific children study is preferable
- Rarity of disorder makes inclusion of children extremely difficult

- The limited number of available children are already enrolled in a nation-wide pediatric disease network
- Study design precludes direct applicability to children
- Insufficient adult data to judge potential risk for children
- Study design is a follow-up of an adult study

The current NIH definition of children includes all persons less than 18 years old. We will exclude potential participants that are younger than the age of 18, as we are conducting this study in adult primary care centers and the PATH intervention is designed for adults.

15. This study involves research to be performed at:

The specific sites are listed below. Each participating site will sign a subcontract or site letter of agreement. The PI and Study Coordinator will be responsible for obtaining or confirming FWA's at all sites prior to any data collection as needed.

Program	Address
Greater Philadelphia Health Action, Inc.	1401 S. 31st Street, 2nd Floor Philadelphia, PA 19146
Whitman Walker Health	Elizabeth Taylor Medical Center 1701 14th St., NW Washington, DC 20009
Wedge Medical Centers	6711 Old York Road Philadelphia, PA 19126
Howard University Hospital Substance Abuse Services	2041 Georgia Avenue Washington, DC 20060

Reminder: It is Principal Investigator's responsibility to obtain copies of FWAs for each performance site.

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