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Design of CLARO (Collaboration Leading to Addiction Treatment and Recovery from other Stresses): A Randomized Trial of Collaborative Care for Opioid Use Disorder and Co-Occurring Depression and/or Posttraumatic Stress Disorder

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Abstract

Introduction: Opioid use disorder (OUD) co-occurring with depression and/or posttraumatic stress disorder (PTSD) is common and, if untreated, may lead to devastating consequences. Despite the availability of evidence-based treatments for these disorders, receipt of treatment is low. Even when treatment is provided, quality is variable. Primary care is an important and underutilized setting for treating co-occurring disorders (COD) because OUD, depression and PTSD are frequently co-morbid with medical conditions and most people visit a primary care provider at least once a year. With rising rates of OUD and opioid-related fatalities, this is a critical treatment and quality gap in a vulnerable and stigmatized population.

Methods: CLARO (Collaboration Leading to Addiction Treatment and Recovery from Other Stresses) is a multi-site, randomized pragmatic trial of collaborative care (CC) for co-occurring disorders in 13 rural and urban primary care clinics in New Mexico to improve care for patients with OUD and co-occurring depression and/or PTSD. CC, a service delivery approach that uses multi-faceted interventions, has not been tested with COD. We will enroll and randomize 900

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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patients to either CC adapted for COD (CC-COD) or enhanced usual care (EUC) and will collect patient data at baseline, 3-, and 6-month follow-up. Our primary outcomes are medications for OUD (MOUD) access, MOUD continuity of care, depression symptoms, and PTSD symptoms.

Discussion: Although CC is effective for improving outcomes in primary care among patients with mental health conditions, it has not been tested for COD. This article describes the CLARO CC-COD intervention and clinical trial.

Keywords

Opioid use disorder; depression; post-traumatic stress disorder; collaborative care; safety net Federally Qualified Health Centers (FQHCs); primary care; integrating primary care and mental health

1. Introduction

Untreated mental illness and substance use disorders are prevalent and can have devastating consequences for the individual, their families and the community.[1–4] Co-occurring opioid use disorder (OUD) with either depression[5] and/or posttraumatic stress disorder (PTSD)[6–8] is of particular concern because depression and PTSD are prevalent in people with OUD, co-occurring mental illness is linked to an increased risk for overdose, and because of the high prevalence of the chronic use of prescription opioids in individuals with mental illness. Such use is a risk factor for transitioning to heroin use and/or the development of an OUD.[9–16] Primary care is an important and underutilized setting in which to provide treatment for all three disorders.[17] However, despite the effectiveness of treatments for all three disorders, many individuals never receive treatment; and, when treatment is provided, quality is low.[18–26] With the rising number of opioid-related fatalities, this is a critical treatment and quality gap in a vulnerable and stigmatized population.

There are multiple reasons for this gap.[27–30] Patients are often not ready for treatment, and there may be psychosocial barriers to engagement and retention. Timely treatment may be difficult to access, and primary care and behavioral health providers may not have needed expertise or certifications.[31] Structural barriers hinder the delivery of integrated treatment. Collaborative care (CC) addresses these problems,[32–34] and studies conducted by our team and others have shown that CC improves access, quality and outcomes in primary care patients with common mental health (MH) conditions. Some studies have shown more tempered results.[35,36] However, CC has never been tested with co-occurring disorders (COD).[37–42]

CC consists of a team of providers that includes a care manager (CM), a primary care provider (PCP) and a behavioral health consultant (BHC), who provide evidence- and measurement-based care to a panel of patients using a clinical registry. In our CC model for COD (CC-COD), the CC team also includes a behavioral health psychotherapist (BHP). Additionally, the evidence-based treatments supported include medications for OUD (MOUD), pharmacotherapy for depression and PTSD, motivational interviewing (MI), problem solving therapy (PST) and Written Exposure Therapy (WET).

This randomized controlled trial (RCT) will adapt and test CC for co-occurring OUD and depressive disorder and/or PTSD (CC-COD). CLARO (Collaboration Leading to Addiction Treatment and Recovery from Other Stresses) is one of four studies funded by the National Institute of Mental Health's (NIMH) HEAL initiative focused on collaborative care for co-occurring disorders.

2. Methods

2.1. Design overview

CLARO is a pragmatic, randomized controlled trial in 13 primary care clinics from three healthcare systems in New Mexico. Figure 1 illustrates the study design and anticipated patient flow from recruitment to enrollment and the evaluation. CLARO tests whether patients with OUD co-occurring with depression and/or PTSD who are randomized to CC-COD have improved access, quality and outcomes, as compared with those randomized to enhanced usual care (EUC). We adapt the CC model to the New Mexico setting and a COD patient population, and use findings on organizational readiness to inform implementation. Primary outcomes include MOUD access; MOUD continuity of care, depression symptoms, and PTSD symptoms. We will assess whether patient experiences of care and working alliance measured at 3 months mediate the impact of CC-COD, and explore whether mental health treatment improves OUD outcomes. Exploratory analyses will look at what factors mediate and moderate the effect of CC-COD. We will also assess contextual factors and implementation outcomes to inform future dissemination if the model is effective.

Under a classification proposed by Curran et al.,[44] our study is a Type 1 effectiveness-implementation hybrid design because we will simultaneously conduct a multi-site trial to determine the effectiveness of CC-COD while also assessing context and implementation. Our trial design is pragmatic,[45] in that it is designed to improve usual practice and inform clinical and policy decisions. These design characteristics include: collaborations with the health care system to adapt the intervention to local conditions, multiple heterogeneous settings, broad patient eligibility criteria that reflect how the intervention will be used in clinical practice, usual care practitioners, multiple outcomes important to decision-makers, intent-to-treat data analysis, and prospective controls.[45–48]

2.2. Study settings and target population.

New Mexico has one of the highest opioid-related overdose death rates,[49] and the U.S. Centers for Disease Control and Prevention projects it will have the highest rates of death from drugs, alcohol and suicide in the nation by 2025.[43] It is a primarily rural state with a Hispanic majority population.[50] CLARO is a collaboration between researchers at the RAND Corporation, the University of New Mexico Health Sciences Center (UNM HSC), and Boston Medical Center (BMC) partnered with three health systems: First Choice Community Healthcare (FCCH, 7 clinics), UNM's Health System (UNM-HS, 3 clinics), and Hidalgo Medical Services (HMS, 3 clinics).

These 13 clinics span three counties, include urban and rural clinics in the regions of New Mexico with the highest rates of opioid overdose (northeast and central) or are primarily

rural (southwest). These organizations and clinics have varying capacity to deliver treatment; for example, the range of buprenorphine prescribers per clinic is 0 to 18. All clinics provide primary care for mostly low-income, predominantly Hispanic patients, and are in Health Professional Shortage Areas for primary care, mental healthcare, or both. Table 1 summarizes clinic and patient characteristics.

We will randomize 900 patients (within each of the 13 participating clinics) who have co-occurring OUD and depression and/or PTSD to receive either CC-COD or enhanced usual care (EUC). All interview data will be collected in REDCap,[51] a secure, web-based Health Insurance Portability and Accountability Act-compliant electronic data capture system by a Statistics and Data Coordinating Center based at UNM.

2.3. Inclusion criteria

Patients will be eligible to participate in the study if they meet the following criteria: receive primary care at one of the 13 clinics, age 18 or older; have a probable OUD diagnosis, defined by scores ≥1 on the self-administered National Institute on Drug Abuse Tobacco, Alcohol, Prescription medication and other Substance use (myTAPS)[53] screener; have probable co-occurring PTSD (having a score ≥3 on the Primary Care PTSD Screen for Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (PC-PTSD-5)[54] or probable depression (a score ≥10 on the Patient Health Questionnaire-9);[55] speak and understand English or Spanish; have capacity to give informed consent; and provide an informed consent electronically or in writing. Pregnant women will not be excluded.

2.4. Exclusion criteria

Patients will only be excluded if they require immediate medical (emergency procedure needed) or psychiatric intervention (i.e., self-injury, active psychosis).

2.5. Baseline assessment

We will include several recruitment strategies across sites. These include anonymous, clinic-population universal screening in clinic waiting areas where and when possible; we cannot currently use this approach due to COVID-19 precautions. Until the pandemic allows reopening, we will primarily rely on referrals from clinic staff, Institutional Review Board approved methods to identify potential participants by examining the electronic health record for individuals with qualifying diagnoses. We will also provide public information about the study through announcements in clinic newsletters, posters in waiting and exam rooms, and a pre-screening questionnaire on the CLARO website with the option of providing contact information for screening. Enrolled patients may refer people (e.g., friends or family) who are receiving primary care at one of the 13 clinics to the study. Some of these strategies are described in more detail in sub-sections below. We plan to take an adaptive approach to determining the optimal recruitment and retention strategies at each of these diverse clinic sites. We will do this by working closely with champions at each clinic and monitoring the enrollment data on a weekly basis to identify the most productive strategies to focus on. Using a variety of methods is key because some of the rural clinics are small, and it would not be cost efficient to station study personnel at them five days a week. It is important to note, due to the SARS-CoV-2/COVID-19 pandemic, there have been changes

to service and patient flow at clinics. Therefore, we anticipate recruitment to vary by site and over time. Adaptations will be made on an as-needed basis, based on our observations, preliminary recruitment success, guidance from the clinical sites and the UNM Office of Research. Regardless of recruitment method, after screening and upon enrollment in the study, participants will complete a baseline assessment interview before being randomized to one of the treatment conditions.

Study subjects will be paid $50 for completing the screening and baseline assessments and will be re-interviewed by telephone three and six months following enrollment with a window of −2 weeks/+4 weeks to conduct each follow-up assessment. They will be offered $40 to complete the 3-month interview and $40 to complete the final interview at 6 months. We will contact patients via phone, text or email to schedule follow-up interviews. We will make multiple attempts at varied times of the day and day of the week during a window period of two weeks prior to the target interview date and four weeks following the target date to contact the participant for each of the two follow-up interviews, and will follow up with hard copy letters to their address, asking them to contact us. We estimate we will be unable to contact up to 20% of enrolled subjects for the follow-up, due to loss to follow-up, incarceration, or death. If all of these methods are unsuccessful, we will ask for help from the clinic staff to contact the patient, and if necessary will contact the patient at the time of one of their scheduled clinic visits.

2.6. Randomization

After a baseline assessment, study participants will be randomized 1:1 to either receive the collaborative care for co-occurring disorders (CC-COD) intervention (n=450), or to receive enhanced usual care (EUC) control (n=450). A stratified randomized block design will be used, with the strata determined by clinic and any prior MOUD exposure. A computer-generated random assignment sequence will be generated for each stratum and will include randomly permuted block sizes of 2 and 4. Research assistants will obtain the patient's intervention allocation from REDCap following completion of the baseline interview. Research assistants, participants, clinic staff, and data coordinating center staff will not be blinded to the intervention assignment; however, all other members of the research team will be.

2.9. Follow-up assessments

Research staff, blinded to subject condition, will conduct an electronic health record review to assess study outcomes. We will abstract data on MOUD use, pharmacotherapy and psychotherapy treatment of depression and/or PTSD, and quality of care for OUD, depression, and PTSD. We will collect follow-up data via telephone interviews at 3 and 6 months after enrollment. The interviews will be approximately 45 minutes long.

We anticipate we will collect utilization data from the electronic health record from 100% of subjects. For the telephone survey, we plan for up to a 20% loss to attrition at follow-up. We recognize that the hardest subjects to reach might provide fundamentally different responses than members of the group who are relatively easier to find, introducing non-response bias and threatening the quality of statistical analyses and the validity and generalizability of

research findings. We will use two categories of methods to increase retention: strategies to stay in touch and strategies for locating "lost" respondents. We will collect extensive contact and re-contact information at study enrollment, providing incentives including remuneration and reminder gift items.

3. Study conditions

There are two study conditions, CC-COD and EUC. Both approaches are hypothesized to be feasible to implement in primary care settings that deliver care with limited resources to diverse patients with complex needs.

3.1. EUC

We carefully considered the comparison condition in conversations with our clinical partners and determined that all patients and providers must have access to the basic elements necessary to provide the continuum of care for COD, including training in the supported treatments. A cluster RCT was not feasible because of the large sample size, and with patient-level randomization, it is not ethical to withhold these basic features of care. Additionally, our clinic partners told us that all treatments must be available to all patients at a given clinic. Thus, EUC includes availability to both the evidenced-based psychotherapy (i.e., Problem Solving Therapy for depression[56] and Written Exposure Therapy for PTSD[57]) and pharmacotherapy (i.e., MOUD and psychotropic medications for depression/PTSD) provided in the CC-COD intervention. The primary difference is the absence of a care management team to coordinate care using a clinical registry for patients in EUC.

3.2. CC-COD

We adapted the traditional CC model to address COD (Table 2). The CC-COD intervention emphasizes the core principles of CC including: patient-centered care (shared decision-making with the patient), population-based care managed through a clinical registry, measurement-based treatment to target using thresholds on clinical outcome measures (e.g., administering symptom management questions at each patient encounter to assess program and adjust treatment plan as needed), and evidence-based psychotherapy and pharmacotherapy treatments[58] (see Table 3 & Figure 2). The intervention is based on a service delivery approach that uses multi-faceted interventions to improve access and quality of care. It is based on Wagner's Chronic Care Model[59,60] and subsequent modifications.[40,61] We hypothesize that the intervention will improve access to the supported evidence-based treatments including MOUD,[62,63] medication treatment for depressive disorders and/or PTSD, motivational interviewing (MI), problem solving therapy (PST) for depression, and written exposure therapy (WET) for PTSD, and that receipt of these treatments will lead to improved clinical outcomes.

In each session, Care Coordinators follow the acronym BALL that stands for build engagement, assess social needs and symptoms, link to care, and loop back with the care team. The Care Coordinator uses MI to assess treatment experiences and barriers to care, provides information about treatment options, and then coordinates next steps with the patient. After the care initiation visit, Care Coordinators will meet with the patient in

monitoring visits for the remainder of the six-month intervention period. Care monitoring visits are similar to initiation visits but are shorter. Care Coordinators will meet with patients individually for at least 13 visits over six months. In the first two months, the Care Coordinator will meet weekly with the patient. In month three, they will meet biweekly. In months four through six, they will meet with patients once a month. Visits can be in-person or by phone, and ideally in-person prior to the PCP visit so that the Care Coordinator can relay information to the PCP before their visit (e.g., symptoms, insights regarding barriers to care). Visits can also be conducted more frequently or for longer than six months should the care team decide it is best for the patient.

The Care Coordinator is supported by a behavioral health consultant (BHC) and a Care Coordinator supervisor with expertise in supervising community health workers. The Care Coordinator meets with BHC and Care Coordinator supervisor, respectively, on a weekly basis to discuss the Care Coordinator's patient caseload.

Finally, Care Coordinators enter patient information into a clinical registry on an ongoing basis. This registry documents a Care Coordinator's patient caseload and has four main purposes:[65] (1) tracks population-level outcomes and engagement (see Table 4), (2) prompts the Care Coordinator with reminders and alerts to ensure accountable outreach when patients have upcoming appointments or need a higher-level of care, (3) prompts treatment-to-target through ongoing symptom management scores that show trends over time in real-time and flags the Care Coordinator when to consult with the BHC, and (4) facilitates caseload review between the Care Coordinator, BHC, and Care Coordinator supervisor through caseload-level reports that display patient-level identification numbers of those who should be discussed.

3.3. Training and supervision

Primary care providers (PCPs).—PCPs who do not have a Xwaiver were offered a 4-hour waiver training to qualify them as buprenorphine waivered practitioner to treat opioid use OUD. Subsequent to the initial training, Physicians then completed an additional 4 hours of online training to quality for a total of 8 hours. Physician Assistants, Nurse Practitioners, and Certified Nurse Midwives completed an additional 20 hours of online modules for a total of 24. The training was sponsored by University of New Mexico's Department of Psychiatry & Behavioral Sciences, Division of Community Behavioral Health (CBH) as part of the Providers Clinical Support System (PCSS), a collaborative effort led by the American Academy of Addiction Psychiatry (AAAP) across the nation.

Behavioral health providers (BHPs).—BHPs are Master's or Doctoral-level therapists who received training on Problem Solving Therapy (PST) to treat depression and Written Exposure Therapy (WET) to treat PTSD. BHPs were trained 2–3 months before the study launch to allow ample time to finish the full course of ongoing training prior to the start of the RCT. For both therapies, BHPs were trained through 6 hours of workshops delivered virtually across two days (3 hours each). Following the PST training workshop, there was an additional 4 hours of individual and group practice sessions for case review (including at least 2 audio recordings) and supervision by the PST developer. After the WET workshop,

BHPs complete 2 cases and attend a minimum of 8 consultation meetings with the WET developer. In total, each BHP will devote at most 40 hours to the trainings; they were provided release time to complete them. Beyond the full course of each training, it is not planned for continued supervision once the trial starts though we will train new BHPs who come onboard during the intervention period.

Care Coordinators.—CHWs will be prepared for the role of Care Coordinators. They will receive at least 40 hours of training that correspond to the five core principles of collaborative care. Specifically, Care Coordinators will receive didactics on the symptoms underlying OUD, depression, and PTSD, and what evidence-based approaches will be offered in CC-COD to treat these illnesses. Care Coordinators will also receive a half-day MI training and will participate in several interactive exercises and role-plays to practice MI in the context of their rehearsal of CC-COD initiation and monitoring visits. Finally, Care Coordinators will receive training where they will learn to administer the measurement-based care questions, interpret findings to aid treatment planning, track patients in the registry (population-based care), and facilitate communication with the patient and members of the care team. Competency will be assessed while observing practice role-play sessions and through audio recordings of patient interactions upon starting the clinical trial.

In addition, Care Coordinators will receive weekly individual reflective supervision. Reflective supervision focuses on reflection between the Care Coordinator and the supervisor to builds on the Care Coordinator's use of her thoughts, feelings, and values within a service encounter.[66] Care Coordinators also participate in weekly group supervision with a BHC using the Extension for Community Healthcare Outcomes (ECHO) model,[67–71] a group videoconference to conduct case conferences.

4. Measures

Our primary outcomes focus on use of MOUD and changes in PTSD and depression symptoms. We will also examine a variety of secondary/exploratory outcomes; mediators and moderators of treatment quality and outcomes; and costs of the CC-COD condition. We will collect measures through baseline/follow-up assessments, electronic health record (EHR) data extraction, and study records. All measures are summarized in Table 5.

4.1. Primary outcomes

We focus on four primary patient outcomes in CLARO. The primary outcomes are: (1) *MOUD access*,[72] defined as patients with a new episode of OUD care (i.e., no care for at least 60 days prior) receiving an MOUD prescription within the first 30 days of that care episode; (2) *MOUD continuity of care*,[73] which refers to the maximum numbers of continuous (i.e., no breaks of more than 7 days) days the patient is prescribed MOUD in the 180 days after study enrollment; (3) *depression symptoms*, as measured by the PHQ-9);[55] and (4) *PTSD symptoms*, as measured by the PTSD Checklist (PCL-5).[74] MOUD continuity and access will be based on prescription (date and frequency) data from the EHR, supplemented by New Mexico Prescription Monitoring Program data if feasible; these measures are well-established metrics for evaluating MOUD quality of care[72,73]. Depression and PTSD symptoms will be collected in baseline and follow-up assessments,

with primary outcome analyses based on change in raw scores across the six-month period (although we will analyze symptom change using other approaches as part of secondary outcomes).

4.2. Secondary/exploratory outcomes

Given the extensive scope and complexity of the CC-COD intervention, we will examine numerous additional outcomes of interest related to substance use and mental health symptoms, health service utilization and quality, and general patient functioning. These include measures of substance use, mental health symptoms, mortality, service utilization, access, quality, and functioning. Details about these measures are provided in Table 5.

4.3. Moderators/patient characteristics

A number of patient characteristics could moderate CC-COD outcomes. Some characteristics will be measured at baseline only; others will be measured in follow-ups as well, either because they could have a time-varying interaction with the intervention or because the most current information is needed for records retrieval (e. g., National Death Index). Moderator variables include (1) *demographic characteristics* (i.e., sex, and ethnicity) (2) *alcohol use severity*, measured for the past 3 months at baseline using the full 10-item AUDIT;[77] (3) *history of MOUD treatment*; and (4) *homelessness*, measured using the Homelessness Screening Clinical Reminder Tool[85] and an item from the Government Performance and Results Act[86] clarifying where individuals who are homeless are currently living.

4.4. Mediators

During the 3-month follow-up assessment, we will measure key care processes thought to mediate the effects of CC-COD on patient outcomes at 6 months, including three measures from the Agency for Healthcare Research and Quality's Consumer Assessment of Healthcare Providers and Systems[87] survey items: (1) *clinician (i.e., Care Coordinator) communication*, (2) *ability to quickly access treatment*, and (3) *satisfaction with treatment*. We will also measure fourth mediator: *patient-Care Coordinator working alliance* using a modified Working Alliance Inventory.[88]

5. Data analysis

5.1. Overview

We will report descriptive statistics at the patient level by study arm. We will present categorical data as frequencies and percentages, and continuous data as means and standard deviations. We will conduct all primary statistical analyses using the intention-to-treat population based on randomization methods to compare CC-OUD with EUC (described in greater detail in Section 5.3).

5.2. Sample size and power

Our study was designed based on power calculations for the four primary outcomes described in Section 3.1. All calculations were for 80% power at a Type I error rate of

1.25%, which accounts for the multiple primary outcomes using a Bonferroni correction to control the family-wise error rate at 5% (0.05/4 = 0.0125). All calculations assumed 900 total study participants and, if relevant, 20% loss to follow up. Additional assumptions for the power calculations were: (1) at enrollment, 50% of study participants will have a new OUD episode of care, defined as no visits with an OUD diagnosis in the past 60 days; (2) at enrollment, one third of study participants will have probable depression, one third will have probable PTSD, and one third will have both probable depression and PTSD; (3) at enrollment, 25% of patients[41] with a new OUD episode of care who receive enhanced usual care will initiate medication for OUD within 30 days of study enrollment; (4) among those who initiate medication for OUD who receive enhanced usual care, the mean number of days of continuous treatment for OUD is 80 with a standard deviation is 65 (personal communication, Asa Wilks); (5) among those with probable depression at enrollment (PHQ-9 ≥ 10), assume a mean depression symptoms score (PHQ-9) of 12 and standard deviation of 6; and among those with probable PTSD at enrollment (PCL-5 > 33), assume a mean PTSD symptoms score (PCL-5) of 50 and standard deviation of 11.

Based on the above assumptions, we will have 80% power to detect a 15 percentage point increase in MOUD access defined as initiation of medication for OUD within 30 days of study enrollment. A previous study of collaborative care for opioid and alcohol use disorders found a 22 percentage point increase over enhanced usual care.[41] We will have 80% power to detect 14 additional days of continuous OUD treatment within the first 180 days. A growing body of evidence suggests that MOUD treatment is associated with decreases in mortality.[89] For depression symptoms, we will be able to detect a 2-point reduction on the PHQ-9. This provides power to detect effects below the clinically important difference for individual change of 5 points.[90] For PTSD symptoms, we will be able to detect a 3.5 point reduction the PCL-5. A previous study of delivering PTSD treatment in primary care setting to active duty military found a reduction in PTSD symptoms of 7 points.[91]

Dropout is of minimal concern in this study, as all analyses are intention-to-treat. For the outcomes based on self-reported symptoms, i.e., depression symptoms and PTSD symptoms, we expect a 20% loss to follow up. This loss to follow up has been accounted for in the power calculations. The sample size (n=900) also provides sufficient power for secondary outcomes.

5.3. Statistical analysis

The primary analyses will be performed for the intention-to-treat population, which consists of all randomized subjects. All statistical hypotheses will be tested using two-sided tests, with adjustment for multiple testing using a Bonferroni correction.

5.3.1. Primary outcomes—Primary outcomes will be analyzed at a Type I error rate of 1.25% to control the family-wise error rate at 5% (0.05/4=0.0125). All primary outcomes will be analyzed with a regression models that includes a clinic-level fixed effect, an indicator for any prior MOUD exposure, and an indicator for the random treatment assignment. Binary outcomes will be analyzed using logistic regression. All other outcomes will be analyzed using linear regression. Outcomes derived from the follow-up surveys are

subject to nonresponse, and statistical hypotheses based on these outcomes will be tested using nonresponse weighted regression models. Specifically, a logistic regression model will be specified predicting response using baseline information, clinic, and the randomization assignment. Nonresponse weights derived from this model will then be used in subsequent analyses.

5.3.2. Secondary outcomes—We will group secondary outcomes into domains of conceptually related outcomes, and each will be analyzed adjusting for multiple comparison within domain. Planned domains are as follows: (1) MOUD treatment (MOUD initiation and MOUD engagement); (2) mental health (access to treatment for depression and/or PTSD; quality of care for depression; quality of care for PTSD and depression remission/response, PTSD remission/response, suicidality); (3) substance use (drug use frequency, alcohol use severity, opioid use severity, opioid overdose risk behaviors, opioid overdose events); and (4) overall health (all-cause mortality, physical health functioning, mental health functioning). We will analyze these secondary outcomes using similar approaches as described for the primary outcomes, but utilizing logistic regression for dichotomous outcomes where appropriate.

5.3.3. Moderators and mediators—In moderator analyses of subgroups, we will explore the data to understand if any of the baseline factors moderate the effect of the intervention. Statistical hypotheses testing whether the effect of the intervention varies by these factors will be tested by the inclusion of an interaction between the moderating factor and the treatment assignment into the previously described models.

In mediator analyses, we will assess whether patient experiences of care and working alliance with the care coordinator at 3 months mediate the impact of CC-COD on patient outcomes, and explore whether mental health treatment at 3 months improves OUD outcomes. To ensure a proper temporal ordering of the treatment, mediators, and outcomes, all outcomes for the mediation analyses will be measured at 6-months, while the mediators will be measured at the 3-month follow-up. All mediation analyses will follow the approach described in Imai, et al. (2010),[92,93] including the technical assumptions necessary to identify causal mediation effects. This methodology requires the specification of a model predicting the mediator using only baseline information, and a model predicting the outcome using both baseline information and the mediator.

6. Discussion

OUD is prevalent, frequently co-occurs with depression and/or PTSD, and is associated with serious consequences. In 2015–16, there were over two million adults with a current OUD; 62% had a co-occurring mental illness and 24% had a co-occurring serious mental illness.[20] While individuals with COD are more likely to receive MH treatment than OUD treatment, only 16–25% report receiving treatment for both conditions.[20,24] Depression and PTSD are two of the most common MH co-morbidities in people with OUD, and when present, are associated with poorer outcomes.[5–7,93–98] Both depression and PTSD are leading causes of disability, and mortality from OUD continues to rise.[1,100]

The CLARO study, one of four NIMH-funded research studies focused on collaborative care for OUD and co-occurring mental health disorders, will help address this problem by improving access, quality, and outcomes of care. These four studies were funded in October 2019 and will run for five years. We expect that findings from these studies will make a substantial contribution to furthering knowledge about the management of OUD co-occurring with mental health problems in primary care settings.

Primary care is an important and underutilized setting in which to identify and provide treatment, but utilization and quality of OUD and behavioral health care is at times low.[100–102] Although specialty OUD care plays a critical role for individuals with severe disease, limited availability, the stigma associated with using specialty care, and a host of other barriers means that specialty care alone is unlikely to be able to address the unmet need for treatment.[104,105] Recent federal legislation[105,106] increased coverage for OUD treatment in primary care, and the prevalence of OUD is high among primary care patients.[108,109] Primary care is also an important source of behavioral health care.[110] Community health centers are of particular importance because they are the largest source of primary health care for underserved individuals and 1 in 12 people in the U.S. receives primary care in a community health center.[111] Using a multi-faceted CC model within these primary care settings has potential to increase access and quality of care because CHWs will help coordinate care that is team-oriented to deliver evidence-based pharmacotherapy and psychotherapy.

It will be challenging to implement and deliver collaborative care for COD. The CLARO settings are diverse, with varying capacity and resources to address COD. There is a need for culturally and linguistically appropriate services, particularly in this minority-majority state. In addition, a host of barriers to care further complicate treatment initiation in rural and low-resource areas, including long distances between patients' homes and clinical sites, over-burdened primary care systems, very limited availability of nursing care and psychiatric care, and the stigma of both substance use disorders and mental illness.

CLARO modifies traditional collaborative care to address some of the known barriers to implementation. CHWs, rather than nurses, are used to provide care management services, and may help increase access by being from the local community. CLARO incorporates telephonic patient follow-up, leverages the scarce resource of psychiatric specialists by using the ECHO model, and incorporates care for substance use disorder and mental illness into primary care in order to decrease stigma. For example, a systematic review identified 28 studies indicating that negative attitudes of health care providers towards individuals with substance use disorders contributes to worse health care provision for these patients.[112]

The undertreatment of OUD is arguably the most important public health problem related to the opioid crisis. In 2015, 11.5 million individuals reported misusing opioids and 1.9 million reported being addicted to opioids,[113] yet fewer than 20% receive any treatment.[114,115] Medication treatment for OUD saves lives, yet at least half of all rural counties in the United States lack a buprenorphine provider, and almost one third of rural Americans (compared with 2.2% of urban Americans) live in a county with no buprenorphine provider.[116] Individuals with COD face similar problems, with fewer than 25% reporting receiving

treatment for both conditions. By experimentally testing a new approach—CC-COD—and assessing implementation factors such as provider acceptability and feasibility, this study could improve public health by identifying an efficient and generalizable model to increase COD treatment delivery and decrease the downstream effects of untreated substance use disorder and mental illness. Our research will advance science by testing collaborative care in a new population and examining whether patient engagement mediates improved outcomes.

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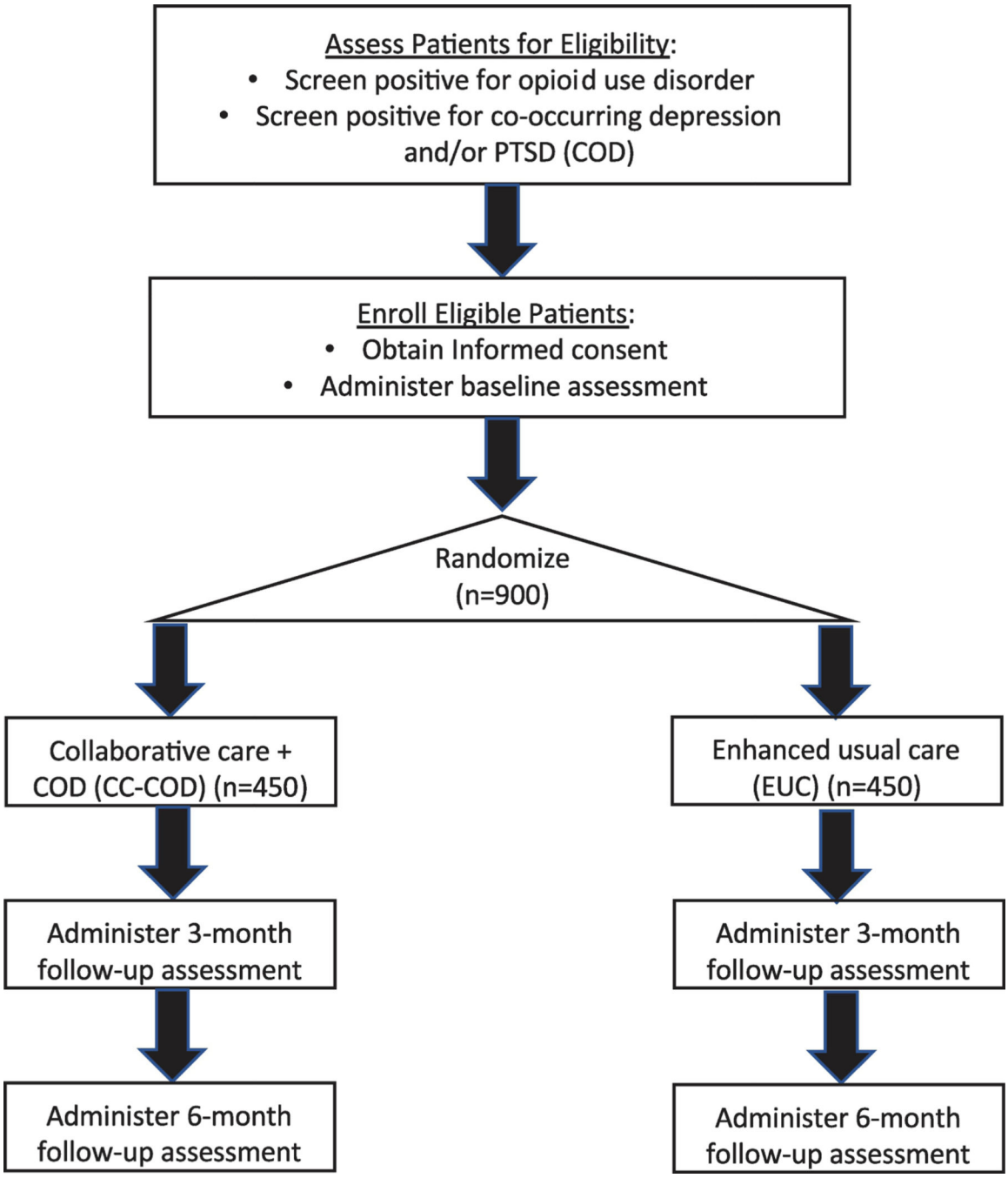

Figure 1.
Overview of study design

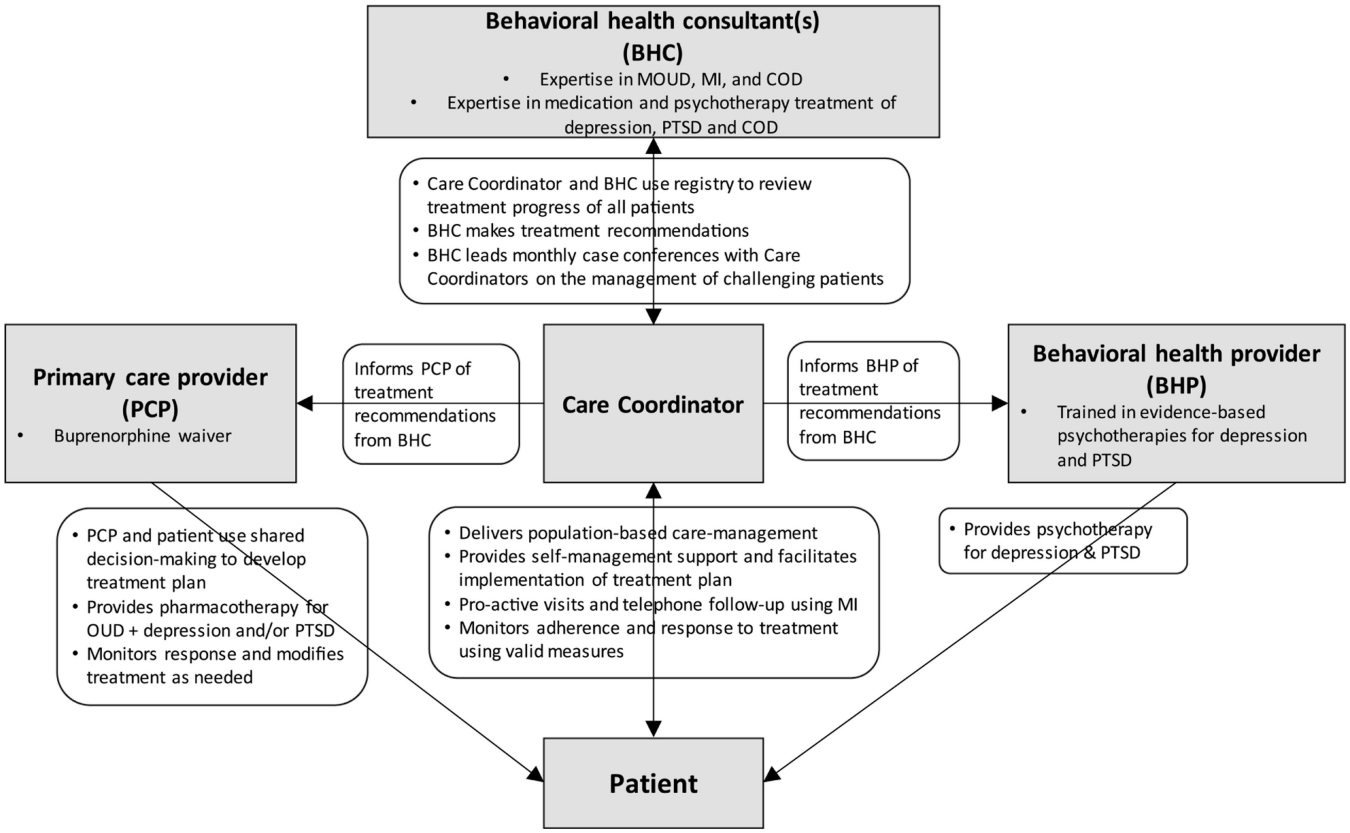

Figure 2.
Overview of CLARO Collaborative care intervention

Table 1.

Characteristics of Clinics and Patient Populations Participating in CLARO

	Organization/Clinic												
Clinic Characteristics													
	First Choice Community Health Care (FCCH)							UNM			Hidalgo Med. Services		
Alamosa	**Belen**	**Edgewood**	**Los Lunas**	**N.Valley**	**S.Broadway**	**S.Valley**	**SE Heights**	**North Valley**	**Southwest Mesa**	**CHC**	**Lordsburg**		**Me Squ**
Health region of NM	central	central l	NE	central l	central	central	central	central	central	Central	SW	SW	SW
Rural per HRSA/HPSA	no	part	part	part	no	no	no	no	no	no	yes	yes	yes
County	Bernalillo	Valencia	Santa Fe	Valencia	Bernalillo	Bernalillo	Bernalillo	Bernalillo	Bernalillo	Bernalillo	Hidal go	Grant	Gra
HPSA primary care	no	yes	yes	yes	no	no	no	no	no	no	yes	yes	yes
HPSA mental health	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
FQHC	yes	yes	yes	yes	yes	yes	yes	no	no	no	yes	yes	yes
# of PCPs (FTEs)	5	3	5	5	5	6	11	6	3.5	3.25	2	4	7
# of onsite BHPs*	2	1	2	1	1	3	4	2	0.7	2	3*	1	4*
Access to staff psychiatrist	limited	limited	limited	limited	limited	limited	yes	yes	Yes	limited	limited	limited	lim
# waivered providers*	5	2	3	0	3	3	7	18	6	5	1	2	2
# of Care Coordinators*	2	2	2	2	2	1	4	3	1	2	0	0	0
Screen for OUD	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Screen for depression	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Patient Demographics													
% Hispanic	87	68	32	75	67	75	89	43	52	67	53	53	53
% African American	3	2	<1	<1	3	4	2	5	<1	<1	1	1	1
% Asian	<1	<1	<1	<1	2	1	<1	23	<1	<1	<1	<1	.<1
% Native American/AK native	1	2	<1	1	1	1	1	2	<1	<1	<1	<1	<1
% Women	57	57	57	63	55	59	58	63	63	63	55	55	55
% Uninsured	15	13	6	13	11	15.5	18	3	5	6	8	8	8
% Medicaid	69	>50	40	66	66	63	65	72	29	46	28	28	28
% Monolingual Spanish	40	19	4	26	16	33	39	19	8	24	3	7	3

UNM=University of New Mexico; HRSA=Health Resources and Services; HPSA=Health Professional Shortage Area; NE=north east; SW=south west; AK=Alaskan.

[*] May not be full-time as providers work across sites. limited=available by phone for consultation.

Table 2.

Traditional Collaborative Care (CC) and CC for Co-Occurring Disorders (CC-COD)

Traditional CC	**Characteristic of population, setting and organization that necessitate change to the traditional CC model**	**CC-COD Modification**
Patients have only one disorder; Care Coordinator provides psychotherapy	Patients have at least 2 and possibly 3 complex disorders, making it difficult for a single Care Coordinator to provide BH treatment for all three conditions.	Add a psychotherapist as part of the CC-COD team (BHP); addresses clinical complexity of patients.
Nurses are in the Care Coordinator role	Setting is HPSA; nurses expensive and scarce, PCPs have large caseloads; Clinical population is impoverished and may prefer to work with a Care Coordinator who is “more like them”; may be ambivalent about treatment.	Care Coordinator is a “trained up” community health worker (addresses nursing shortage) who uses MI and is able to make home visits; leverages scarce professional resources; may address stigma experienced by population.
Psychiatrists are available to work with Care Coordinator in person and have the necessary expertise	Scarcity of professional resources with addiction and psychiatric expertise; Multiple co-morbidities make it difficult for single expert consultant to have all necessary expertise; Geographic remoteness.	Use of ECHO and monthly multi-disciplinary case conferences that include pharmacotherapy and psychotherapy experts in addiction and mental illness (BHCs); addresses geographic remoteness and need for interdisciplinary expertise; leverages scarce resources.

BH=Behavioral Health; BHC=Behavioral Health Consultants; BHP=Behavioral Health Provider; EHCO=Extension for Community Healthcare Outcomes; HPSA=Health Professional Shortage Area; PCP=Primary Care Provider.

Table 3.

Description of How Core Principles are Integrated in the CC-COD Intervention

Core-principles	CC-COD intervention
Patient-centered care[117]	• Shared decision-making between the care management team and patients where problems to address are clearly defined, treatment plans are mutually agreed upon (e.g., initiation visit uses a menu of options to do this), and barriers are identified and addressed (e.g., social needs)
	• Designation of a community health worker as Care Coordinator to engage the patient, actively monitor their progress, make necessary modifications to the treatment plan, and link them to care
Measurement-based treatment to target	• Routine symptom monitoring through measurement-based care and goal attainment questions to assess progress
	• Adjusting treatment plans by progress with the goal of symptom remission for all conditions
Population-based care	• Use of registry to track a caseload of patients
	• Use of registry flags that inform Care Coordinators/supervisors/consultants of patients in need of higher-level care (e.g., patients with missed visits, suicidality)
	• Use of registry to track patient progress by symptoms (e.g., MBC) and service receipt (e.g., MOUD, WET, PST)
Evidence-based care	• Offering MOUD, WET, and PST to treat OUD and depression/PTSD
	• Using MI to deliver care initiation and monitoring visits
	• Monitoring initiation, engagement, and retention of MOUD, WET, and PST

CC-OUD=Collaborative Care for Opioid Use Disorder; MBC=Measurement-Based Care; MOUD=Medication for Opioid Use Disorder; PST=Problem-Solving Therapy; PTSD=Post-Traumatic Stress Disorder; WET=Written Exposure Therapy.

Table 4.

CC-COD Intervention Visit Measures

SCALES	NO. OF ITEMS	SYMPTOMS ASSESSED	WHEN TO ADMINISTER
WellRx[64]	11	Social determinants of health	At 1st visit
OUD-5	5	Opioid cravings, medication side effects, withdrawal, substance use	Every visit
PROMIS-7	7	Cravings, interpersonal challenges related to substance use, severity of use	At 2nd visit and once per month
PHQ-9	9	Depression symptoms	At 2nd visit and once per month (if applicable)
PCL-5	20	PTSD symptoms	At 2nd visit and once per month (if applicable)
PEG	3	Pain severity and interference	As needed
ISI		Insomnia symptoms	As needed

OUD=Opioid Use Disorder; PROMIS=Patient-Reported Outcomes Measurement Information System; PHQ=Patient Health Questionnaire; PCL-5=PTSD Checklist; PEG=Pain, Enjoyment, General Activity; ISI=Insomnia Severity Index; PTSD=Post-Traumatic Stress Disorder.

Table 5.

CLARO Evaluation Measures, Data Collection Schedule, and Source of Data

Measure	Pre	3M	6M	Operational Definition	Source
Eligibility Criteria					
Probable OUD diagnosis	X			myTAPS score ≥ 1[53]	IAS
Probable depression	X			PHQ-9 score ≥ 10 [55]	AS
Probable PTSD	X			PC-PTSD-5 score ≥ 3 [54]	AS
Age 18 or older	X			n/a	AS
Patient at participating clinic	X			Receiving primary care at one of the 11 participating clinics	AS
Speak English or Spanish	X			n/a	AS
Primary Outcomes					
MOUD access *[72]	X	X	X	Receipt of MOUD prescription within 30 days	MR
MOUD continuity of care[73]	X	X	X	Max number of continuous days on MOUD (i.e., no breaks of more than 7 days)	MR
Depression symptoms	X	X	X	PHQ-9 (change in raw score)	IAS&TS
PTSD symptoms	X	X	X	PCL-5 [74] (change in raw score)	IAS&TS
Secondary Outcomes					
Drug use frequency	X	X	X	Days of use in past 30 days for prescription opioids, heroin, cocaine/crack, methamphetamine/other stimulants, and tranquilizers/sedatives (NSDUH[75] items)	IAS&TS
Opioid use severity	X	X	X	PROMIS Substance Use Short Form[76] for past 30 days	IAS&TS
Alcohol use	X	X	X	AUDIT-C[77] for past 3 months	IAS&TS
Urine drug screen	X	X	X	n/a	MR
Opioid overdose risk behaviors	X	X	X	Opioid Overdose Risk Assessment[78]	IAS&TS
Opioid overdose events	X	X	X	Naloxone Overdose Baseline Questionnaire[79]	IAS&TS
Depression remission	X	X	X	PHQ-9 score < 10	TS
Depression response	X	X	X	PHQ-9 score < 50% of baseline score	TS
PTSD remission	X	X	X	PCL-5 score < 34	TS
PTSD response	X	X	X	PCL-5 score < 50% of baseline score	TS
Severe suicidality	X	X	X	Columbia Suicide Severity Rating Scale,[80] dichotomized based on presence vs. absence of a plan, intent, and/or attempt	IAS&TS
All-cause mortality		X	X	Death records[81]	NDI
MOUD initiation *		X	X	Receipt of MOUD prescription within 14 days of diagnosis[82]	MR
MOUD engagement *		X	X	Receipt of two or more MOUD prescriptions within 34 days of diagnosis[82]	MR
Access to treatment for depression and/or PTSD		X	X	Receipt of medication and/or behavioral treatment associated with diagnosis	MR
Quality of care for depression *		X	X	4 psychotherapy visits in the first 8 weeks or an adequate (12-week) medication trial	MR
Quality of care for PTSD *[83]		X	X	4 psychotherapy visits in the first 8 weeks or an adequate (60-day) medication trial	MR
General health functioning[84]	X	X	X	Veterans RAND 12-item Health Survey (VR-12)	IAS&TS
Moderators/patient characteristics					
Demographics	X			(sex, race, ethnicity, education level, marital status)	IAS

Measure	Pre	3M	6M	Operational Definition	Source
Alcohol use severity	X	X	X	AUDIT[77] for past 3 months	IAS
Pain levels	X	X	X	PEG Pain Monitor[118] for past week	IAS&TS
History of MOUD treatment	X			items developed by the research team	IAS
Current depression/PTSD treatment	X			NSDUH[75] items	IAS
Prior experiences with a Care Coordinator	X			items developed by the research team	IAS
Interpersonal support	X			Presence of a support person who does not have problematic opioid use	IAS
Homelessness	X			Homelessness Screening Clinical Reminder Tool;[85] GRPA[86] item	IAS
Legal involvement	X	X	X	NSDUH[75] items; Addiction Severity Index[119] items	IAS&TS
Disability and impairment	X			Sheehan Disability Scale[120]	IAS
Rurality	X	X	X	Rural-Urban Commuting Area[121] code associated with ZIP code	IAS&TS
Mediators					
Clinician (Care Coordinator) communication		X	X	CAHPS	TS
Ability to access treatment quickly		X	X	CAHPS	TS
Satisfaction with treatment		X	X	CAHPS[87]	TS
Patient-Care Coordinator working alliance		X	X	Modified form of Working Alliance Inventory - General Practice[88]	TS

myTAPS = self-administered Tobacco, Alcohol, Prescription medication, and other Substance use screener; PHQ = Patient Health Questionnaire; PC-PTSD-5 = Primary Care PTSD screener for DSM-5; PCL = PTSD checklist for DSM-5; NSDUH = National Survey on Drug Use and Health; PROMIS = Patient-Reported Outcomes Measurement Information System; AUDIT = Alcohol Use Disorder Consumption Test; AUDIT-C = AUDIT consumption questions; CAHPS = Consumer Assessment of Healthcare Providers and Systems; AS = anonymous screening; IAS = interview administered survey; MR = medical record; TS = telephone survey; NDI = National Death Index; MOUD = medication for opioid use disorder.

*Outcome only assessed for patients with a new episode of care. A new episode of care for OUD is defined as no MOUD care in the previous 60 days. A new episode of care for depression or PTSD is defined as no visits associated with the respective diagnosis in the previous six months.