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A Patient-Centered Nurse-Supported Primary care-based Collaborative Care Program to Treat Opioid Use Disorder and Depression: Design and Protocol for the MI-CARE Randomized Controlled Trial

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Abstract

Background.—Opioid use disorder (OUD) contributes to rising morbidity and mortality. Life-saving OUD treatments can be provided in primary care but most patients with OUD don't receive treatment. Comorbid depression and other conditions complicate OUD management, especially in primary care. The MI-CARE trial is a pragmatic randomized encouragement (Zelen) trial testing whether offering collaborative care (CC) to patients with OUD and clinically-significant depressive symptoms, increases OUD medication treatment with buprenorphine and improves depression outcomes, compared to usual care.

Methods.—Adult primary care patients with OUD and depressive symptoms (n≥800) from two statewide health systems: Kaiser Permanente Washington and Indiana University Health are identified with computer algorithms from electronic Health record (EHR) data and automatically enrolled. A random sub-sample (50%) of eligible patients is *offered* the MI-CARE intervention: a 12-month nurse-driven CC intervention that includes motivational interviewing and behavioral activation. The remaining 50% of the study cohort comprise the usual care comparison group and is never contacted. The primary outcome is days of buprenorphine treatment provided during the intervention period. The powered secondary outcome is change in Patient Health Questionnaire (PHQ)-9 depression screening scores. Both outcomes are obtained from secondary electronic healthcare sources and compared in "intent-to-treat" analyses.

Conclusion.—MI-CARE addresses the need for rigorous encouragement trials to evaluate benefits of *offering* CC to generalizable samples of patients with OUD and mental health conditions identified from EHRs, as they would be in practice, and comparing outcomes to usual primary care. We describe the design and implementation of the trial, currently underway.

Trial Registration: ClinicalTrials.gov Identifier: NCT05122676. Clinical trial registration date: November 17, 2021

Keywords

Opioid Use Disorder; Depression; Collaborative Care; Primary Care; Motivational Interviewing; Behavioral Activation

INTRODUCTION

Opioid use and its sequelae have contributed to widespread morbidity and mortality, with the COVID-19 pandemic bringing a sharp rise in opioid-related deaths and related morbidity.[6–8] Effective treatments for opioid use disorder (OUD) are grossly underutilized, with uptake hampered by widespread shortages of behavioral health and primary care (PC) services.[9, 10] Treatments with medications for OUD (MOUD) including buprenorphine, methadone or injectable naltrexone (XR-NTX) decrease illicit opioid use and overdose risk while improving overall health.[11–16] However, access to methadone treatment programs is severely limited, many addiction treatment programs do not offer MOUD, and stigma prevents most people from seeking specialty OUD treatment. Most people with OUD can be effectively treated with buprenorphine and XR-NTX in PC[14, 15, 17–19] and providing treatment in PC may lower access barriers. Primary care providers (PCPs) can also treat common co-occurring disorders like depression, anxiety, pain,[4, 20] other substance use disorders (SUDs), and insomnia that act as barriers to OUD treatment and can contribute to relapse.

Despite the potential benefits of PC provision of MOUD, treatment is not available in most PC settings.[21] About 80% of people with OUD seen in PC are not treated for OUD[22, 23] and 80% of PCPs do not want to prescribe buprenorphine, likely reflecting structural barriers (e.g. lack of coverage), time and workflow limitations (e.g. fitting care into brief PC appointments), stigma, and PCP concerns about treating OUD without systems to support high quality care.[14, 21] Effective OUD treatment is also complicated by the high prevalence of comorbid conditions including depression and other SUDs.[24–26] The stigma associated with OUD may discourage patients from seeking treatment or disclosing their OUD symptoms,[27] and those prescribed opioids may worry about losing their pain medication. Patient-centered engagement is therefore critical to increasing access to treatment in non-treatment seeking patients with OUD. No effective approach is known to engage non-treatment seeking patients with OUD, and little research has targeted this important issue.

Collaborative care (CC) may be able to increase initiation and engagement of primary care patients with OUD. The CC model was developed over thirty years ago to address failures in depression treatment in PC.[28] CC is a model in which care managers working from the chronic disease model[29] and supported by expert consultants, are able to enhance PCP's delivery of effective treatment. The CC model includes 5 components: population-based PC, patient-centered team-based care, evidence-based care, measurement-based care (MBC) with treatment to target, and accountability.[30] In practice, CC adds to the PC team both a care manager and a psychiatric consultant to provide proactive, high quality, planned care with evidence-based treatments over time.[28] CC improves outcomes for depression, other mental health disorders, pain,[31, 32] and potentially alcohol use disorder.[33–37] but no study has demonstrated the effectiveness of CC for OUD.[34, 36, 37] However, nurse care management has been associated with increased PC access to OUD treatment[38, 39] and adding a CC care manager to support the PC team has the promise of overcoming many of the OUD treatment barriers described above.

Testing whether CC interventions increase OUD treatment initiation and engagement in non-treatment-seeking patients with OUD requires pragmatic trial designs. Most CC trials for behavioral health conditions have been efficacy or effectiveness trials that randomized patients after consent.[40] The treatments evaluated in such traditional clinical trials may yield quite different outcomes from real world treatment. Patients willing to enroll in a trial may be more motivated than others to work with a care manager and hence, may have different outcomes compared to patients offered CC as part of routine care. Additionally, conventional trials cannot evaluate whether proactive outreach from a nurse care manager (NCM) offering CC results in overall PC population benefit/impact among all patients with OUD, including non-treatment seeking patients.[41]

This pragmatic trial seeks to fill these gaps by testing the hypothesis that CC can both increase OUD treatment and improve depression outcomes. *The More Individualized Care: Assessment & Recovery through Engagement* (MI-CARE) trial is a randomized encouragement (Zelen) trial that will test whether offering 12 months of telehealth CC from a nurse addressing OUD, depression, and common associated conditions (e.g. mental health and substance use disorders, chronic pain, and sleep problems), can increase OUD treatment and improve depression outcomes among adult PC patients with recent electronic health record (EHR) documentation of: (1) clinically significant depressive symptoms and (2) evidence of active OUD documented in the prior year. MI-CARE is one of four studies funded by the National Institute of Mental Health's (NIMH) HEAL initiative[42] focused on CC for OUD and co-occurring conditions.

METHODS

Study/Design Overview

The study objective is to evaluate the effectiveness of offering eligible PC patients the MI-CARE CC program compared to usual PC. Among eligible PC patients ($n \geq 800$), we will assess the following outcomes during the 12-month intervention:

- Days of buprenorphine medication treatment for OUD in the year after randomization (Aim 1).
- Change in depressive symptoms on the Patient Health Questionnaire (PHQ-9) score in the year after randomization (Aim 2)

Given the limitations of conventional trial designs described in the introduction, this study adopts an encouragement/Zelen design[43–46] in which all patients receiving care in participating healthcare systems (HCSs) who are eligible for the study cohort are identified using EHR data, randomized, and followed passively using electronic data sources, as in an observational study. A random sub-sample (50%) is selected from this cohort to be offered CC services, thus encouraging such patients to engage in the telehealth CC program. The remaining 50% from the study cohort are a true "usual care" comparison group. To avoid measurement bias, outcomes data are collected entirely from secondary electronic sources (e.g., EHR, insurance claims data prescription monitoring programs). The entire eligible PC cohort is included in the analysis, including those who decline participation in CC. The defining feature of an encouragement/Zelen design is random treatment assignment prior

to consent, allowing the inclusion of a sample of patients with stigmatized conditions who may be unlikely to seek treatment or agree to participate in a conventional trial. Further, this design allows evaluation of patient engagement with a CC intervention offered as part of routine care The overall study design and trial participant flow is depicted in Figure 1. We hypothesize that patients randomized to be offered MI-CARE CC, compared to the usual care arm will (1) have a significantly greater number of days of buprenorphine treatment over the 12-month follow-up (primary outcome), and (2) have a greater reduction in depressive symptoms on the PHQ-9 during follow-up (powered secondary outcome).

Informed consent considerations

To maximize validity and generalizability, we chose an encouragement/Zelen design[43] to include non-treatment seeking patients who otherwise would not be included in a traditional randomized trial. This design requires waivers of consent and HIPAA authorization for eligibility screening and enrollment, as well as a general waiver of consent to use secondary data for outcomes in both arms. The consent process for the CC program is designed to mimic oral consent practices for clinical care, augmented by elements of consent for human subject's research (e.g., program offered is part of research, participation is optional, declining will not affect access to usual care, patients can stop participating in CC at any time). Therefore, a waiver of documentation of consent and an alteration of consent is also needed.

Study settings and sample

Participants will be enrolled from two health care systems (HCSs) representing different delivery types and geographical regions – Kaiser Permanente Washington (KPWA) and Indiana University Health (IUH). KPWA is an integrated care delivery system that provides insurance coverage and care to a defined patient population in 32 PC clinics. IUH includes approximately 90 PC clinics that utilize both integrated care and fee-for-service payment models. Both HCSs provide medical and mental health care across urban, suburban, and rural areas of their respective states. Patients are representative of each system's geographic service area in terms of race, ethnicity, education, and income. Both systems use the PHQ-9 questionnaire[47] to assess depression in outpatient clinics. The study sample includes PC patients ≥18 years with:

1. recent EHR documentation of clinically significant depressive symptoms (PHQ-9 ≥10) and
2. evidence of OUD documented in the prior year (Table 1). We will enroll at least 800 patients across the two HCSs in approximately equal proportions.

Enrollment and randomization

Database queries at each HCS are used to identify patients who meet eligibility criteria during the previous week (See Table 1). Queries are run weekly during the recruitment period except when paused to manage NCM workload, refine computer codes, or perform data quality checking. Automatically within the sampling computer program, all eligible patients are randomly assigned (1:1, stratified by HCS) to continue in usual care or to be

offered the MI-CARE CC program. A computer-generated concealed allocation table at each site provides randomly generated assignments in block sizes of 4,6, and 8.

Engagement of patients randomized to CC intervention

The MI-CARE CC program prioritizes patient-centered, non-stigmatized engagement followed by shared decision-making. Outreach practices are designed to align with how patients are approached, assessed and engaged in clinical care. Patients are then offered an opportunity to decide if the program interests them. A key part of engagement is assessment of OUD symptoms, patient-recognition of OUD, and readiness for treatment. Some patients are expected to not have active OUD (e.g., opioid dependence may have been documented to indicate physiologic dependence on prescribed opioids), and some patients may not recognize or may be uncomfortable divulging OUD symptoms initially. Developing an outreach process that was acceptable to patients and enhances engagement was a critical objective of a brief MI-CARE pilot study (more information on the pilot study is included in the Supplement). Outreach procedures—designed to engage and avoid offending patients who may not identify with OUD—include the following key elements:

- ***EHR review***. NCMs review each intervention arm patient's chart to identify their PCP and mental health clinicians (if applicable).
- ***Initial message to PCP***. PCPs are sent an EHR message informing them their patient is eligible for MI-CARE and inviting them to send information about the program to the patient. If the patient is closely followed by a mental health provider, s/he may also be notified. If an established PCP is not evident, the NCM outreaches the patient and offers to help them establish a PCP.
- ***Initial patient approach***. Eligible patients are sent a message via the EHR web portal or by mail. The communication allows patients to opt out before being called by the NCM. This initial message does not mention OUD, instead focusing on depressive symptoms ("stress and low mood") and things that impact them like pain, sleep, medications, or substance use for people who take or have taken opioids.
- ***Administering oral consent to patients***. Patients who do not opt out are phoned by a NCM to offer the CC program and obtain oral consent, which includes a brief description of the study purpose, study procedures, potential risks, and the right to decline participation in the CC program. A written study information sheet is sent via the patient's preferred method (email, texted weblink, mail) after verbal consent is obtained.

We expect that readiness to engage in CC and in buprenorphine treatment will vary from patient to patient and over time. We intentionally mirror the way such a program would be offered in actual practice, allowing patients to disengage at any time, and to reengage if and when they choose during the 12-month intervention period. Thus, unless patients both refuse the intervention and to be contacted at a later time, study NCMs continue to outreach periodically. Specifically, NCMs are asked to outreach not yet consented patients three times a week, several times a day over the first two weeks, then every other week with this same

cadence through 6 weeks, and monthly thereafter (persisting through to 10–11 month of the 12-month active intervention period).

Usual care condition

When participants are assigned to usual care, neither they nor their PCPs are ever contacted by study staff.

Study Intervention

The MI-CARE CC intervention emphasizes the five core components identified in the CC model originally designed to improve mental health outcomes in PC.[30] Table 2 describes how these core elements are integrated into the MI-CARE intervention. Table 3 summarizes how this approach has been adapted to meet the needs of: (1) our encouragement/Zelen study design, (2) this population with multiple co-occurring conditions including OUD, depression, and other common possible comorbidities (e.g. chronic pain, and other SUD and mental health conditions), and (3) the infrastructure, clinical resources, and clinical practice processes within the HCSs in which the MI-CARE CC intervention is embedded.

The MI-CARE intervention is designed as a centralized, telehealth-driven approach administered by a NCM using audio or video technology. In addition to supporting PCP in initiating and adjusting medication treatment for target (OUD and depression) and frequently associated (e.g., other mental health, substance use, chronic pain, and sleep) conditions, the CC approach includes NCM use of two core non-pharmacotherapy approaches, motivational interviewing (MI) and behavioral activation (BA). MI is often used by healthcare providers to help patients identify and resolve ambivalence about changing their behavior.[48] MI works by activating patients' own motivation for change and adherence to treatment.[49] BA is a brief structured treatment for depression aimed at increasing rewarding and productive experiences, which can be delivered by individuals without previous experience delivering psychotherapy services.[50–52] BA is considered transdiagnostic because its core components are useful for a variety of problems where avoidance is common.[53–55]

Figure 1 includes a depiction of the clinicians involved in the MI-CARE CC team. The NCM role, CC consultants, and systems of care (e.g., MBC measures, MI-CARE patient registry) are designed to support patients and PC teams virtually. Medical treatment is provided (per usual) by licensed PCPs and other clinicians in the participating HSCs. NCMs are encouraged to meet with patients weekly when initially engaging the patient in MI-CARE CC, when establishing or changing treatment, if using BA, or as needed to re-engage or help stabilize a patient (e.g., suicidality, overdose). Over the 12-month intervention period, monthly telehealth sessions are the targeted interval as care becomes established for stabilized patients. Patient reported outcome measures are administered by NCMs soon after the patient has consented to participate in MI-CARE CC to support engagement, patient self-recognition of symptoms, diagnostic impressions, and provide a baseline for MBC. Table 4 includes core MBC assessments used in the MI-CARE intervention (Table A in the supplement includes the comprehensive set of assessments used clinically in the trial). NCMs discuss measure scores, changes over time, and their meaning with patients; use

score changes as part of MBC—an indicator of treatment response (or lack thereof and need to adjust treatment); and document MBC scores in EHRs for PC team members.

NCM Training and Supervision

Initial NCM training consists of approximately 6.5 days on main intervention components including: medication management of OUD (2 half-day trainings on Office Based Addiction Treatment [OBAT]); CC, MBC and medication management (2 half day trainings); training in crisis protocols and safety planning (half day); and training in the use of MI and BA (8 hours spread over 4–8 weeks with out-of-session practice).

NCMs in each HCS meet weekly with a CC team that includes a psychiatrist and a PCP experienced providing MOUD in PC. Each CC team includes an addiction-boarded physician. The CC team uses a registry to provide supervision on each NCM's panel.

NCMs are also supported in a weekly or biweekly meeting (and via ad-hoc phone or email consultation) by national OBAT nurse experts at Boston University.[39] The NCMs have weekly or biweekly group meetings with psychologists to support their use of MI, BA, crisis response, safety planning, and general issues. NCMs also record their patient visits and a sample of these are listened to by psychologists and reviewed in 1:1 feedback sessions at least twice a month.

Primary and Powered Secondary Outcome and their Sources

All quantitative outcome measures are obtained from secondary health services information (e.g., EHR, claims, health information exchanges and state prescription monitoring programs). This is necessary because 50% of enrolled patients are randomized to usual care and are never contacted by the study and those randomized to CC are followed irrespective of engagement.

The primary trial outcome is a continuous measure of days of buprenorphine treatment in the 365 days after randomization. This measure reflects both MOUD initiation and retention, is attainable as secondary data in both HCSs, reflects first-line office-based MOUD treatment, was used in another large pragmatic trial,[58] and aligns with the core outcome set for OUD treatment research from a recent Delphi process by the NIDA Clinical Trials Network.[59] We measure buprenorphine treatment for the primary outcome using pharmacy and insurance claims data on dispensed buprenorphine in KPWA, and EHR buprenorphine orders and claims data available in IUH. We are also making every effort to obtain prescription monitoring program (PMP) data from Indiana and Washington state for our primary outcome analyses as it is the most comprehensive and unbiased source of this data.

The powered secondary outcome for this study is a change in depressive symptoms from the study qualifying PHQ-9 score to a follow-up PHQ-9 score documented as part of clinical care in EHR 3–13 months later (imputed from the 2-item PHQ if necessary and including PHQ-9s documented in the EHR by nurses to support high quality CC at one site).The PHQ-9 is a well-validated and widely used tool to assess for depression in PC that is

currently used for routine screening in both participating healthcare systems.[56, 60–62] Other secondary outcomes are described in Table 4.

Analysis plan

Main analyses will be conducted following an intention-to-treat (ITT) approach, including all randomized individuals in the analysis—both CC and usual care, and irrespective of engagement for those randomized to CC.

For the primary outcome, we will use a linear regression analysis adjusted for the baseline value, health system, and other pre-specified covariates measured pre-randomization. From the regression model we will estimate the mean difference in days of OUD treatment comparing patients randomly assigned to each trial arm. Standard errors will be calculated using the robust (sandwich) variance estimator[63] given the non-normally distributed outcome. If we are able to obtain PMP data but data sharing restrictions limit our ability to conduct a pooled analysis (including both health-systems data) our back-up plan is to conduct a distributed data analysis, pooling health-system specific estimates.

For the powered secondary outcome— change in depressive symptoms—we will use the PHQ score closest to 12 months from randomization in the event of multiple PHQ-9s. A simulation study– to be completed prior to obtaining any outcome data – is planned to confirm that this approach is unbiased given the potential for differential measurement of the outcome across the intervention and control arms because CC includes documentation in the EHR. Following a similar approach as for the primary outcome, we will use a linear regression analysis of the change score (follow-up PHQ-9 score minus baseline score), adjusted for baseline score, HSC, time from randomization to follow-up score, and other pre-specified covariates measured pre-randomization. From the regression model we will estimate the mean difference in the PHQ change score comparing patients randomly assigned to each trial arm. Standard errors will be calculated using the robust (sandwich) variance estimator.

For both the primary and powered secondary outcome, the set of baseline variables that will be adjusted for will be selected using simulations based on pre-trial data to identify variables associated with the outcome (to increase statistical precision and power). These will be pre-specified in the standalone statistical analysis plan (SAP) prior to obtaining any outcome study data. Analyses of other secondary outcomes are exploratory and are outlined in the Supplement.

Sample size

Table 5 summarizes the minimal detectable difference (MDD) in the mean number of days of buprenorphine treatment (primary outcome) and change in depressive symptoms (powered secondary outcome) with 80% power comparing intervention versus control using ITT analyses. MDDs are presented under different values of the R^2 of included baseline covariates (ranging from R^2 of 0 [corresponding to no prognostic covariates] to 0.4 [corresponding to more highly prognostic covariates]). These calculations use a two-sided type 1 error rate of 0.05.

For our primary outcome, we estimated we will have 80% power to detect a difference in the mean number of days of buprenorphine treatment of 20 days, assuming a standard deviation (SD) of 98.3 (based on preliminary data) and a sample size of 760 patients (assuming 5% of the target 800 are missing outcome data). Because we expect half or more of patients randomized to the intervention arm will not engage, this intervention effect (among all randomized patients) is attenuated by those not getting the intervention for whom we expect similar treatment and response to treatment as usual care (mean number of days of 46.7).

For our powered secondary outcome, we estimated we will have 80% power to detect a ≥1.72 point difference in the PHQ change score between intervention and usual care, assuming a standard deviation of 6.7 (based on preliminary data) and a sample size of 480 (assuming a 60% PHQ follow-up rate). For engagement rates of at least 35%, or for lower engagement rates combined with highly prognostic baseline characteristics, we estimated we will have sufficient power to detect a difference of ≥5 for change in PHQ between engaged patients versus usual care patients (smaller in some scenarios). A prior study found a change between 2.59–4.78 to be the minimal clinically important difference (MCID)[64], leading to a commonly defined threshold of 3–5 points for the MCID.[65–68]

Formative evaluation

Throughout the trial, all aspects of intervention delivery and NCM supervision are monitored and iteratively reviewed to improve NCM care and CC supervision (see Supplement).

Ethical and regulatory approval

Institutional Review Board (IRB) oversight is provided for the study by a single IRB (sIRB) at Advarra (Protocol No. 00045256) with individual IRBs for each of the HCSs ceding local authority yet reviewing for local context. In addition, we ensure materials and procedures align with HCS and regional care standards. The participating IRBs agreed that the study presented minimal risk because offering additional care that supports receipt of evidence-based practices is minimal risk and such outreach and care management for chronic conditions are often used in study HCSs.

Oversight and Safety Monitoring

A data and safety monitoring board (DSMB) established by NIMH convenes to monitor and advise on the study-related participant safety and data quality. The DSMB meets three times per year to review reports from the study; no interim analyses are planned. While there are no strict stopping rules, the DSMB and sIRB have authority to stop or alter study procedures as needed to ensure participant safety.

Due to the pragmatic study design, adverse events (AEs) in the control arm are not observed by NCMs. Therefore, AEs and serious AEs (SAEs) systematically reported to the DSMB must rely on data sources available and collected uniformly across both study arms. All reportable events, including adverse events, follow guidelines set forth by the national Office for Human Research Protections (OHRP) and the sIRB.

A NCM may learn of the death of a patient during outreach for those randomized to the CC study arm. Deaths are not unexpected in the target population and are promptly reported along with an assessment of potential relatedness to CC.

DISCUSSION

The trial addresses a practical question that is relevant to practicing clinicians and health system leaders: Will population-based outreach programs that offer a PC-based CC program increase OUD treatment and improve depression outcomes among those with clinically significant depression symptoms and evidence of an OUD diagnosis? Central pragmatic trial features that reflect real world clinical issues and, hence, strengthen the external validity of the study include:

- ***Population-based PC sample***: MI-CARE not only evaluates CC for patients with OUD and depression in the sample who would be offered the program—allowing assessment of reach—but also allows the trial to assess whether CC might increase access to buprenorphine treatment, in addition to improving the quality of OUD and depression care for patients offered the MI-CARE CC intervention.
- ***Generalizable PC sample***: The trial has broad inclusion and narrow exclusion criteria, testing a model that includes systematic evidence-based detection and care for concomitant disorders when indicated.
- ***Allowing variable CC intervention participation***: The intervention is designed to be flexible, allowing patients to engage when they are ready, and for as long as possible or helpful for them, as in routine clinical care.
- ***Comparison to a "no-contact" usual care control***: Outreach and assessment can activate patients and change their behavior.[69, 70] MI-CARE's encouragement/Zelen design allows evaluation of the benefit of CC compared to the alternative: usual PC. This is possible due to use of EHR and other electronic data to define the sample and outcomes.
- ***Intent-to-treat analyses***: A rigorous evaluation of CC program effectiveness examines outcomes among all eligible patients.

Despite the above pragmatic features, our trial differs from a purely pragmatic design in at least one important aspect: the training and supervision of the NCMs delivering the CC intervention. Interdisciplinary training and support is substantial and ongoing throughout the trial (5 hours early in the trial now decreased to 2.5 hours a week). This training and supervision is necessary because the NCM clinical role for this trial requires implementation of new clinical work processes. If the MI-CARE CC program is proven effective, we would recommend that any subsequent implementation include a similar level of training and regular supervision for nurse care managers.

There are limitations of our approach that merit comment. First, the downside of our encouragement/Zelen design is our restriction to use of secondary clinical data for identifying the study sample and all study outcomes and covariates. Consequently, we have

less diagnostic precision than studies directly assessing study participants. Further, we may have missing data if participants leave the participating HCS's or do not complete follow-up PHQs during the study period. Second, having our NCMs working telephonically presents challenges to developing close partnership with PC teams. However, such an approach may improve effectiveness, and is important to evaluate given the increased adoption of telehealth practices post-pandemic.[71] Finally, although our study sites are in regions of the country heavily impacted by the opioid crisis, neither Washington State nor Indiana reflects the diverse population characteristic of the country.

MI-CARE follows the core principles of pragmatic trials: population-based enrollment, broad generalizable sample, variable treatment participation, no contact with the comparison arm participants, assessing outcomes using EHR data, and analyses based on intent-to-treat. We hypothesize that patients randomized to be offered MI-CARE CC, compared to usual care, will (1) have a significantly greater number of days of buprenorphine treatment over the 12-month follow-up (primary outcome), and (2) have a greater reduction in depressive symptoms on the PHQ during follow-up (powered secondary outcome). This encouragement design trial is currently underway in two large HCSs. Our results will fill important gaps in our understanding about the effectiveness of CC for OUD and depression approaches in real-world PC settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

OUD	opioid use disorder
MOUD	medication treatment of opioid use disorder
PCP	primary care provider

SUD	substance use disorder
CC	collaborative care
NIMH	National Institute of Mental Health
PHQ-9	9-item Patient Health Question
MBC	measurement-based care
HCS	healthcare system
IUH	Indiana University Health
KPWA	Kaiser Permanente Washington
NCM	nurse care manager
CBT	cognitive behavioral therapy
MI	motivational interviewing
BA	behavioral activation
MDD	minimal detectable difference
ITT	intent to treat analysis
SD	standard deviation
MCID	meaningful clinically important difference
AE	Adverse Event
EHR	electronic health record
sIRB	single institutional review board
OHRP	Office for Human Research Protections
DSMB	data safety and monitoring board
OBAT	Office Based Addiction Treatment

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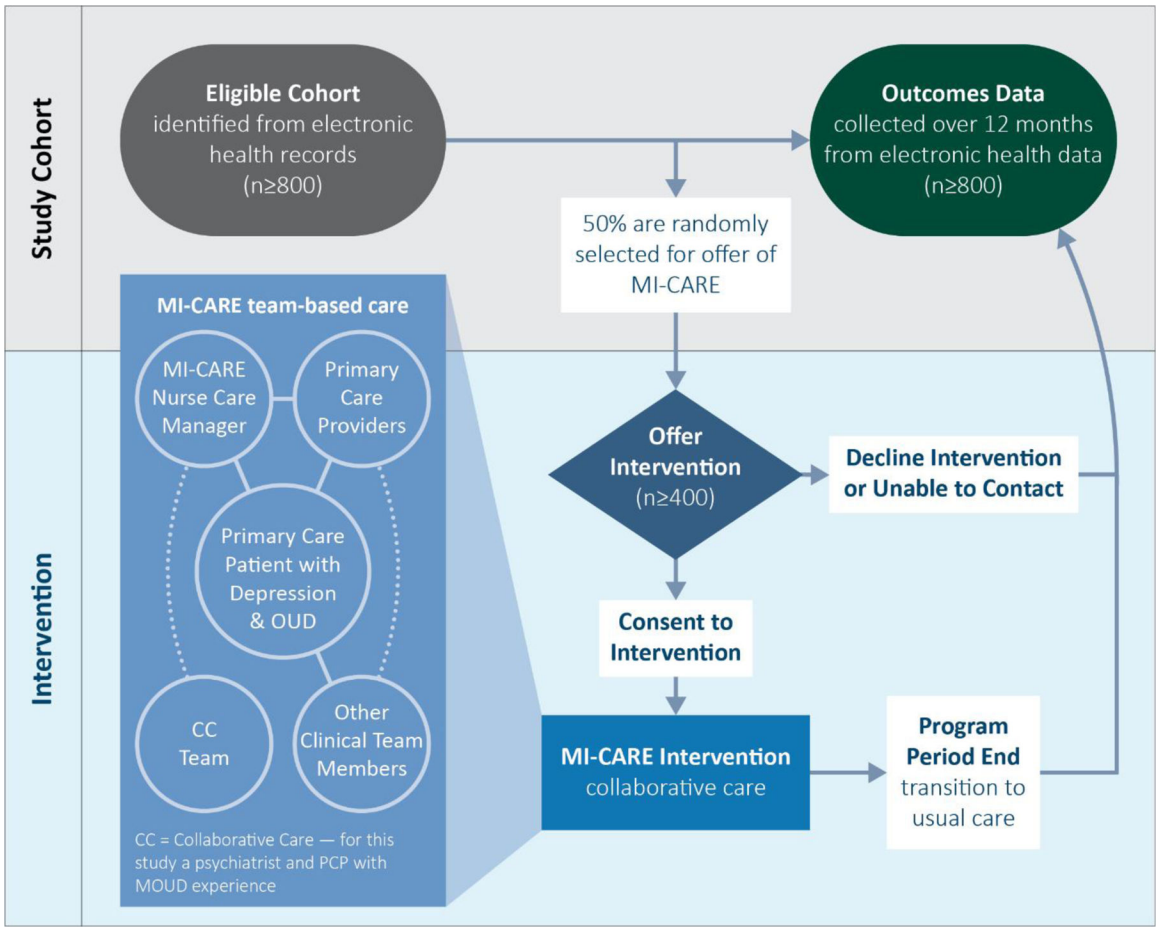

Figure 1.
Overall MI-CARE Study Design and Trial Participant Flow

Table 1.

Inclusion and exclusion criteria for the MI-CARE study cohort

Inclusion Criteria	**Exclusion Criteria**
• 18 years of age or older • PHQ-9 score ≥ 10 in the prior week • PC visit in the HCS in the prior year • Evidence of OUD in the year prior (defined below)	• OUD diagnosis only from 42 CFR Part 2 covered facilities • Patients previously outreached in a small pilot of the MI-CARE trial at both HCSs • Patient requiring English interpretation • Chemotherapy or radiation treatment for cancer (except non-melanoma skin cancers) in the past 3 months • Actively in a related CC program (e.g., depression, anxiety) or requested no participation in research at KPWA
*Evidence of OUD is defined as: • Active OUD ICD-10 diagnosis code • Prescription or procedure code for MOUD • Diagnosed opioid overdose	Patients are also excluded if they have evidence in the prior 2 years of: • Alzheimer's disease or dementia • Severe cognitive limitations. • Hospice care

PHQ-9 = 9-item Patient \Health Questionnaire, PC= primary care, HCS = health care system, OUD = opioid use disorder, CC = collaborative care, KPWA = Kaiser Permanente Washington, MOUD = medications to treat OUD.

*An additional criterion based on opioid use was omitted after several months due to heterogeneity.

Table 2.

Description of Integration of Core Collaborative Care Elements into MI-CARE CC Intervention

Population-based primary care	• Proactive outreach based on a patient registry so that patients don't "fall through the cracks" of primary care • Registry reviewed weekly with CC team to guide nurse care and outreach to primary care and other specialty providers • Registry organized to indicate patient readiness for care (recognition of OUD) and symptoms and reviewed for treatment engagement, response to treatment, and need for potential treatment changes or need for higher level care
Patient-centered team-based primary care	• NCMs use of shared decision-making, eliciting patients' own health narratives, values and priorities, providing information on evidence-based care options and supporting the patients while they decide which treatment(s) is/are right for them • Engagement and NCM visits focused on patient's goals and priorities, and communicates patient preferences and choices, as well as CC consultant recommendations, to the primary care team and other care providers, as appropriate to support the delivery of care • NCM helps patient connect with social services as needed to address resource (e.g., food, stable housing, medical insurance) and safety-related needs (e.g., domestic violence)
Evidence-based care	• NCM supports patients in accessing evidence-based mental health and substance use disorder treatments from the primary care team or specialty behavioral health providers (e.g., medications appropriate for the treatment of OUD, depression, and related problems [e.g., anxiety, sleep problems, chronic pain, unhealthy alcohol use) • Use of motivational interviewing skills to engage patients in treatment and encourage behavioral change • NCM provides behavioral activation targeting depression and related symptoms • NCM follows evidence-based safety planning processes for patients with active suicidality or overdose risk • NCM recommends other evidence-based non-pharmacologic care to patient and primary care team when appropriate and connects patient with care as able (e.g., methadone outpatient treatment for OUD, counseling, peer support, online CBT-based programs for insomnia or chronic pain)
Measurement-based treatment to target	• NCM and CC consultants use systematic clinical measures of patient symptoms (e.g., PHQ-9, etc.) to support treatment and treatment adjustments • Patient reported measures are used to monitor symptoms of OUD, depression, and other conditions (e.g., anxiety, pain, sleep) over time (Table 4 and Supplement Table A) • Worsening or lack of symptom improvement (e.g., craving opioids) guides recommendation for treatment changes
Accountable care	• NCM, expert consultants, and primary care team are responsible for individual patients and population of patients • NCM and consultants review MI-CARE patient registry weekly throughout the follow-up period and identify approaches to improving the quality of care

CC = collaborative care, NCM = nurse care manager, OUD = opioid use disorder, CBT = cognitive behavioral therapy

Table 3.

Adaptations of Collaborative Care Approach for MI-CARE Intervention

Traditional CC	Characteristics of study design, population, and healthcare setting requiring adaptation of tractional CC model	MI-CARE CC modification(s)
Patients with qualifying condition(s) agree in advance to CC treatment	Study focus on offering care to patients who may not seek care nor recognize OUD symptoms by enrolling eligible patients in HCSs pre-consent (encouragement/ Zelen design)	Strong emphasis on MI-guided engagement (trained and supported by psychologists); NCM readiness to support treatment of related disorders that patient might prioritize (e.g., sleep problems, pain) and work to connect to core MI-CARE targets (OUD, depression)
CC care provided within primary care setting predominantly in-person	Large geographic spread of healthcare systems (including rural areas of the state) without nurses in each primary care clinic with expertise to provide this type of CC care; expensive	Centralized, telehealth-driven nurse care manager model
CC typically targets single/ focused behavioral health disorder	Patients have at least clinically significant symptoms of depression and problem with opioids and often other mental health and substance related issues	Adopt more transdiagnostic focus for BA; provide robust training for NCM and ongoing supervision with a range of experts (psychiatrist, primary care Buprenorphine prescriber, OBAT nurses, and psychologists)
Patients with unstable psychiatric conditions often excluded from CC	Patients with multiple complex disorders, vulnerable to frequent and chronic suicidality, and overdose risk	Robust training and supervision in application of safety planning process; ongoing active supervision by psychologists

CC = collaborative care, MI = motivational interviewing, NCM = nurse care manager, OUD = opioid use disorder, HCS = healthcare system, BA = behavioral activation, OBAT = office-based addiction treatment

Table 4.

MI-CARE Intervention Visit Measures and Trial Outcome Measures

Patient-report measures used for measurement-based care (MBC) by NCM (Intervention only)					
Core MBC Instruments		**Items**	**Scoring**	**Timeframe**	**Frequency of Administration**
Patient Health Questionnaire (PHQ-9)	We use the PHQ-9[56] to assess the severity of depression and assesses change over time	9	10–14 moderate 15–19 severe 20–27 very severe	Past 2 weeks	Baseline, target every 2 weeks
Opioid Use Monitor (OUM)	This measure is adapted for OUD from the PROMIS short form for severity of substance use.[57] The past 2-week timeframe is used to match the PHQ-9	7	0–28	Past 2 weeks	Baseline, target for every 2 weeks
Trial Outcomes from secondary electronic data (both trial arms)					

Primary outcome: Days of buprenorphine treatment for OUD in the 1–365 days after randomization

Secondary powered outcome: Change in depressive symptoms from the study qualifying PHQ-9 score to follow-up PHQ-9 score documented as part of routine clinical care 3–13 months later

Other secondary outcomes:

1 A composite of buprenorphine treatment (binary measure of treatment with buprenorphine formulations for OUD or pain defined as > 90 days during the 12-month follow-up) and/or clinically significant improved depressive symptoms (50% decrease in PHQ-9 score or negative PHQ-2)

2 a composite of any major adverse event over 12 months of follow-up (including: opioid overdose, other drug overdose, suicide attempt or other self-harm, hospitalizations [opioid and non-opioid] or death)

3 a count of serious opioid-related events (including emergency department visits or hospitalizations with a primary OUD or opioid-related diagnosis or an opioid-related overdose [lethal or non-lethal]).

PROMIS = Patient Reported Outcomes Measurement Information System, PHQ = Personal Health Questionnaire; PHQ-2 = 2-item Patient Health Questionnaire

Table 5.

Minimal detectable difference (MDD) in main outcomes under various scenarios for engagement rate and prognostic value (R^2) of baseline covariates

R^2 of baseline covariate	MDD of Days of Buprenorphine Treatment for OUD					
	ITT	MDD in the engaged sample given different engagement rates (%)				
		30%	35%	40%	45%	50%
0	20	66.7	57.1	50.0	44.4	40.0
0.1	19	63.3	54.2	47.5	42.2	38.0
0.2	17.9	59.7	51.1	44.8	39.8	35.8
0.3	16.7	55.8	47.8	41.9	37.2	33.5
0.4	15.5	51.7	44.3	38.8	34.4	31.0
R^2 of baseline covariate	MDD in PHQ change score, from baseline to follow-up					
	ITT	MDD in the engaged sample given different engagement rates (%)				
		30%	35%	40%	45%	50%
0	1.72	5.73	4.91	4.30	3.82	3.44
0.1	1.62	5.40	4.63	4.05	3.60	3.24
0.2	1.54	5.13	4.40	3.85	3.42	3.08
0.3	1.44	4.80	4.11	3.60	3.20	3.08
0.4	1.32	4.40	3.77	3.30	2.93	2.64

All analyses assume 80% power, and a two-sided type 1 error rate of 0.05. Analyses of days of MOUD treatment assume a sample size of 760 (5% loss to follow-up) and analyses of change in PHQ score assume a sample size of 480 (40% loss to follow-up). PASS software to compute MDD estimates for the ITT intervention effect (https://www.ncss.com/)

ITT = intention to treat