PATIENT-CENTERED TEAM-BASED PRIMARY CARE TO TREAT OPIOID USE DISORDER, DEPRESSION, AND OTHER CONDITIONS: THE MI-CARE* STUDY

* More Individualized Care: Assessment and Recovery through Engagement

MI CARE

PRAGMATIC TRIAL PROTOCOL

VERSION 9.0

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MULTIPLE PRINCIPAL INVESTIGATORS

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1 PROTOCOL SUMMARY

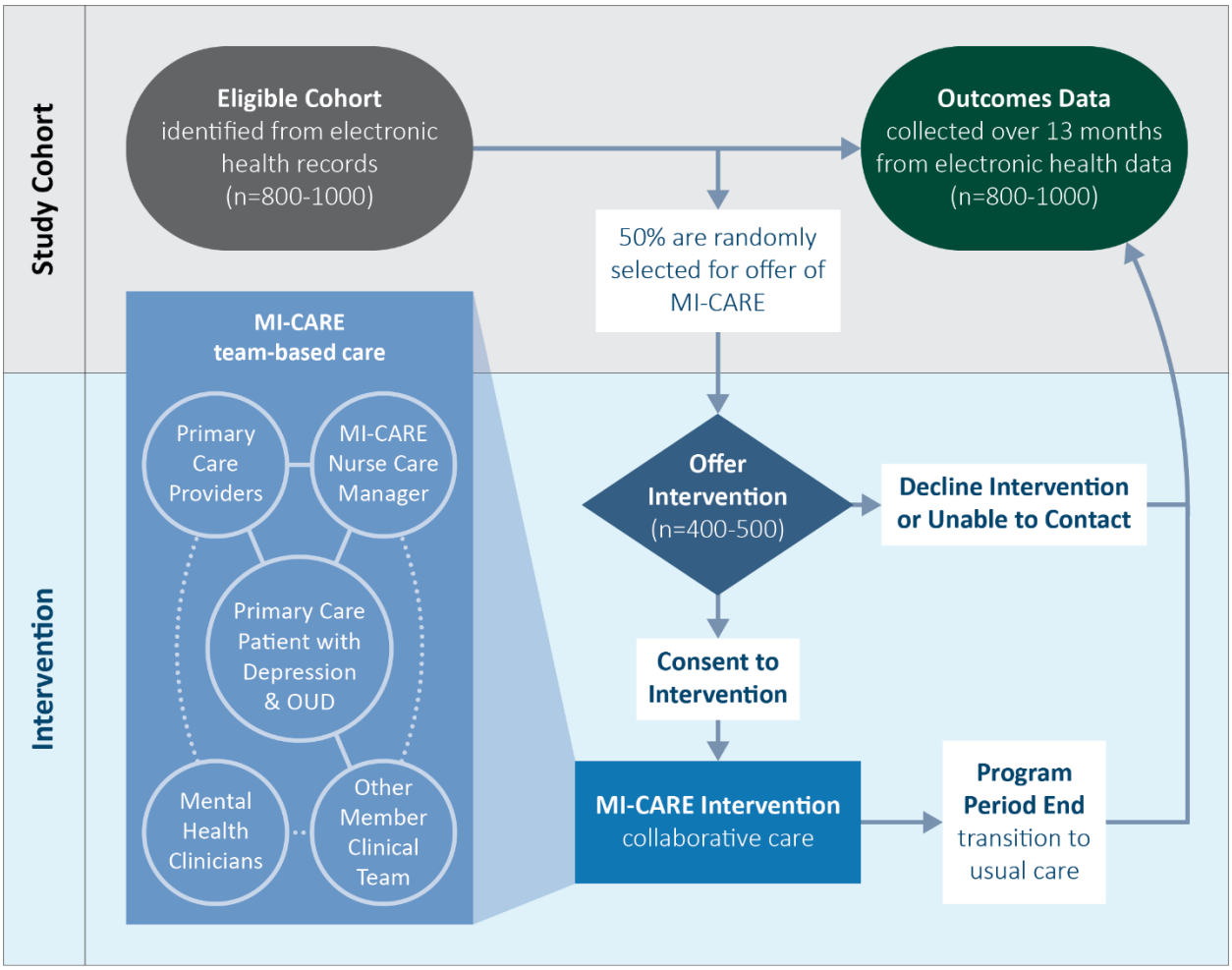
1.1 SYNOPSIS

Grant Title	Patient-centered Team-based Primary Care to Treat Opioid Use Disorder, Depression, and Other Conditions
Intervention and Patient Facing Title	More Individualized Care: Assessment and Recovery through Engagement (MI-CARE)
Précis	The MI-CARE trial is a randomized encouragement trial that will test whether offering a primary care-based collaborative care (CC) model can increase opioid use disorder (OUD) treatment and improve depression outcomes among patients with: a) recent electronic health record (EHR) documentation of depressive symptoms, and b) evidence of OUD documented in the prior year. The trial will automatically identify a total of 800-1,000 primary care patients across two health systems: Kaiser Permanente Washington and Indiana University Health. Half of patients automatically identified as eligible for the trial will be randomly selected to be offered the MI-CARE intervention. A pilot study was conducted prior to fielding the trial to finalize workflows in the two participating health systems, and refine recruitment, engagement and materials but could not assess engagement rates as about half of eligible patients were "hand-picked" for outreach to optimize diversity and inform refinement of the intervention.
Objective	The study objective is to evaluate the effectiveness of offering eligible primary care patients the MI-CARE CC program when compared to usual primary care. Among all eligible primary care patients, MI-CARE and usual primary care will be compared to assess the following outcomes: • Aim 1: Days of OUD medication treatment (buprenorphine) • Aim 2: Improvement of depression symptoms. • Aim 3 (intervention arm only): Examining a) implementation using mixed-methods formative evaluation including reach, adoption, and implementation fidelity, and b) nurse care manager time needed to support the MICARE intervention.
Target Population	Using EHR and claims data we will identify and enroll 800-1,000 English-speaking primary care patients, 18 years and older, with a Patient Health Questionnaire (PHQ) depression score of 10 or higher in the prior week and an indication of OUD in the prior year.
Research Sites	• Kaiser Permanente Washington (KPWA) *(enrollment site)* • Indiana University Health (IUH) *(enrollment site)* • Kaiser Permanente Northwest (KPNW) *(formative analysis, nurse support and training)*
Non-Research Sites	• University of Washington *(nurse support and training)*

	• University of New Mexico *(nurse support and training)* • Boston Medical Center *(nurse support and training)* • Montana State University *(nurse support and training)* • Purdue University *(pharmacoepidemiology consultation)*
Trial Randomization	1:1 (offered intervention: usual care), stratified by site
Study Intervention	The MI-CARE CC intervention is offered by a nurse care manager (NCM) and delivered by telephone (or video) visits to consenting patients. The CC intervention addresses OUD, depression, and other common co-occurring conditions (e.g., pain, sleep, anxiety, suicidality, prescribed opioids or benzodiazepines, other substance use etc.). CC consists of 5 components:[1] • Population-based Care: All eligible patients are managed proactively with outreach and a study patient registry so that patients don't "fall through the cracks" of primary care. • Patient-centered Team Care: The NCM and a primary care team work together to provide patient-centered care. • Evidence-based Care: The NCM supports evidence-based psychosocial and pharmacologic treatments. • Measurement-based Treatment to Target: The NCM uses systematically collected patient reported outcomes to support engagement and treatment adjustments. • Accountable Care. The NCM, the expert consultants at each site, and primary care team are responsible for individual patients and the population of patients.
Usual Care Comparator	Participants in the eligible target population who are not randomized to be offered the MI-CARE CC intervention. Usual care participants have no contact with the study.
Participant Duration	12 months from the date of randomization with 1 additional month allowed for patients to complete any annual PHQ from the health system (13 months, overall).
Outcomes	All outcomes are obtained exclusively from secondary data sources. The trial will test whether patients randomized to be offered the MI-CARE CC intervention, compared to those randomized to usual care: (1) have a significantly greater number of days of medication treatment for OUD over the 12-month follow-up (primary outcome); (2) have a greater reduction in depression symptoms on the PHQ over 12-month follow-up (powered secondary outcome); To support future implementation, the trial will also examine measures of: (3) reach of the intervention, adoption of OUD treatment by primary care providers, and implementation fidelity of the intervention, as well as nurse care manager effort required per patient in CC intervention (CMS billable and nonbillable hours). Secondary outcomes include composite outcomes to assess: (1) Treatment with buprenorphine or clinical response of depressive symptoms;

	(2) Adverse events relating to depression or opioid use (e.g., suicide attempt, overdose, hospitalization, or death); and (3) Serious opioid-related events.
Study Duration	31 months (main trial launch through end of data collection from all sources)

1.2 SCHEMA FOR CLINICAL TRIAL



1.3 SCHEDULE OF ACTIVITIES

ACTIVITY OR EVENT	DESCRIPTION	SCHEDULE
Identify eligible patients from EHR/claims and randomly select 50% to be offered CC (MI-CARE arm)	Eligible adult patients (PHQ score ≥ 10 in the 7 days prior to a given week's data extraction date; OUD diagnosis in prior year) are enrolled in the trial automatically; 50% of the eligible cohort will be randomly selected to be offered the MI-CARE intervention. The "index date" is the randomization date.	Day 0 = Date of randomization
MI-CARE CC ARM ONLY		
PCP and introductory patient recruitment outreach	NCM has initial contact with PCP via standard modes of clinical communication at KPWA and IUH. Patient initial outreach could be by mail, patient web portal, or pre-verified email (IUH only). Initial outreach is followed by phone outreach attempts.	Day 1 (PCP) / up to 4 (patient) – various (may delay patient outreach based on clinical scenario)
Consent patients for MI-CARE program	NCM administers verbal consent by phone. An information sheet is provided after the call.	Day 2 – various
Intervention delivery	Collaborative care program delivered by NCM to consenting participants.	(As earlier as) Day 3 – Day 365
BOTH MI-CARE AND USUAL CARE ARMS		
Participation dates	• Secondary data collection for primary outcome analyses.	Day 0 – Day 365
PHQ participation dates	• Data collection for Aim 2 outcomes involving PHQ data begins day 30 and ends 395 days after randomization. An additional 30 days is allowed for the health system to capture PHQ screening collected on an annual basis.	Day 30 – Day 395

2 INTRODUCTION

2.1 RATIONALE FOR TREATING OUD, DEPRESSION AND OTHER CONDITIONS IN PRIMARY CARE

The United States is in the midst of an opioid epidemic and evidence-based treatment for opioid use disorders (OUD) requires medications.[2,3] While methadone is the oldest treatment for OUD, it can only be provided in specially accredited outpatient treatment programs. Two effective medication treatments for OUD - buprenorphine[4] and injectable naltrexone - can be provided in primary care.[5, 6]

2.1.1 NEED FOR IMPROVED ACCESS TO OUD TREATMENT

Experts recommend that most OUD can be treated with buprenorphine and injectable naltrexone in primary care for several reasons.[2] First, access to methadone maintenance in external outpatient treatment programs is severely limited. Moreover, many specialty "rehab" treatment programs do not offer medications (often due to unfounded beliefs that all medication treatment of addiction is wrong or lack of prescribers on staff). There are also not enough prescribing addictions specialists to treat all patients with OUD, and stigma prevents most people from seeking specialty treatment for OUD.[7] Finally, medication treatment in primary care alone is effective for OUD: adding specialty addictions-focused counseling to medication treatment for OUD has not been shown to improve outcomes.[8] Thus, providing treatment integrated with primary care is logical. It may lower barriers to access, and primary care providers (PCPs) can also treat common co-occurring disorders like depression, pain, and insomnia.

2.1.2 NEED TO INCREASE ACCESS TO TREATMENT OF OUD IN PRIMARY CARE

OUD treatment is not yet accessible in most primary care settings. About 80% of people with OUD seen in primary care are not being treated for OUD.[9, 10] PCPs can be concerned about taking on the complexity of treating OUD without systems to support high quality care. In this way, OUD is akin to anticoagulation or diabetes, or medications for depression: primary care can manage it, but systems are needed to support high quality care.

2.1.3 NON-STIGMATIZED PATIENT ENGAGEMENT IS CRITICAL FOR OUD[11]

Given the stigma associated with all substance use disorders, including OUD, many patients do not disclose their OUD symptoms. Those who have prescription medication OUD may be worried about losing their opioid supply. While some patients with OUD self-refer to primary care-based OUD treatment, if it is available, many others are diagnosed with OUD but do not receive OUD treatment. Patient-centered engagement is therefore critical to increasing access to OUD treatment. However, it has received relatively little focus by researchers.

No effective approach is known for engaging non-treatment seeking patients with OUD in treatment, and little research has targeted this important issue.

2.1.4 HIGHER MEDICATION DOSE AND LONGER RETENTION IN OUD TREATMENT IS ASSOCIATED WITH REDUCED MORTALITY

Higher methadone and buprenorphine dose has been associated with retention and survival.[12] Further, there is a recognized need to improve retention in OUD treatment, ideally 90 days at a minimum, although many experts consider that lifelong treatment is safest. Generally, retention has not been high, with only 25-50% of patients treated with buprenorphine receiving at least 180-days of OUD medication treatment in observational studies.

2.1.5 DEPRESSION AND OTHER COMMON COMORBID CONDITIONS INTRODUCE ADDITIONAL BARRIERS TO OUD TREATMENT

Effective treatment of OUD is complicated by the high prevalence of comorbid conditions including depression, anxiety, pain, insomnia, and other substance use disorders.[13-15] In a sample of primary care patients with OUD, the prevalence of comorbid conditions were: 50% depression, 41% anxiety, 19% insomnia, 82% pain, 31% additional substance use disorders.[16] More than half of patients on medications to treat OUD report chronic pain[17] and, when present, pain is associated with increased opioid craving and illicit opioid use, as well as poor adherence to medication to treat OUD.[18] Many patients with OUD view pain as central to both the onset and maintenance of their OUD symptoms.[19-21] Addressing pain and comorbid mental health and substance use may be critical for treatment engagement and efficacy.

2.1.6 COLLABORATIVE CARE IS A PROVEN MODEL FOR IMPROVING DELIVERY OF EMPIRICALLY SUPPORTED BEHAVIORAL HEALTH TREATMENTS TO PRIMARY CARE PATIENTS

Collaborative care enhances engagement and retention in mental health treatment. The collaborative care (CC) model was developed more than thirty years ago to address failures in the delivery of effective depression treatment.[22] Rather than a treatment in and of itself, CC is a model in which a care manager supports delivery of effective treatment components based on principles of effective chronic illness care. The CC model includes 5 components: population-based care, patient-centered team-based care, evidence-based care, measurement-based care with treatment to target, and accountability. In practice, CC adds both a care manager proactively engaging patients in care management and a psychiatric consultant to the primary care team in order to provide high quality, evidence-based treatments over time.[22] CC has been shown to improve outcomes for depression, other mental health and alcohol use disorders, and pain,[23, 24] but no study has demonstrated the effectiveness of CC for a substance use disorder and mental health condition simultaneously.

2.1.7 COLLABORATIVE CARE FOR OUD ALONE HAS NOT BEEN SHOWN EFFECTIVE IN A TRIAL

CC has also been used to support primary care for OUD and has been found to increase access to OUD treatment.[5] Observational studies of the OUD CC model developed and implemented throughout

Massachusetts suggest that its adoption results in increases in the number of patients treated with buprenorphine (~100 patients/nurse) and impressive retention (12-month retention rates of 67% in community settings).[11] However, this program did not actively outreach or engage non-treatment seeking patients (patients self-referred who wanted treatment). No randomized control trial has demonstrated that offering CC for OUD alone increases access to OUD treatment (i.e., encourages patient engagement in such care) and/or improves OUD outcomes. Several efficacy trials of nurse care management in patients with OUD-alone, who consented to be in the trials, have found no benefit[25-27] for OUD.

2.1.8 COLLABORATIVE CARE FOR OUD COMBINED WITH COMMON COMORBID BEHAVIORAL HEALTH CONDITIONS IS UNTESTED

CC is increasingly being used to address diverse behavioral health conditions, conditions often comorbid with OUD (e.g., depression, anxiety, pain, and alcohol use disorders).[22] Further, research has shown that CC can address multiple conditions simultaneously.[24, 28] However, it is unknown how to optimally integrate CC for OUD with CC for depression, other mental health and substance use disorders, or chronic pain. Moreover, while only ~20% of primary care patients with OUD have EHR-documented OUD treatment, little is known about what proportion would accept OUD treatment if it were offered in primary care. The MI-CARE trial was designed to address that gap and test whether offering CC to patients with OUD and depression would increase OUD treatment in primary care and improve depressive symptoms.

2.2 RATIONALE FOR ENCOURAGMENT TRIAL DESIGN

2.2.1 IMPORTANCE OF TRIALS THAT ASSESS WHETHER OFFERING CC PROACTIVELY TO PRIMARY CARE PATIENTS WITH OUD AND BEHAVIORAL HEALTH CONDITIONS IMPROVES OUTCOMES

Most CC trials for depression and other behavioral health conditions have been efficacy trials that randomized patients after consent. The treatments evaluated in such traditional clinical trials may yield outcomes quite different from outcomes of more typical treatment by real world providers. These trials indicate if CC is effective for those who are interested, but do not assess the population benefit of offering CC. Such trials have important limitations. First, review of published CONSORT diagrams from these studies suggests many had relatively low rates of participation. Thus, while some patients do benefit, many were not interested. However, these low rates of engagement may not be generalizable: there is a difference between being willing to consider care from a CC nurse (e.g., MI-CARE) and being open to participating in a more traditional randomized controlled trial of CC. Evaluating the population benefit is even more important for studying CC for OUD. OUD treatment is more stigmatized than depression. Many patients are not initially interested in medications or other “treatment” for OUD, and many assume that treatment means “going to rehab,” so a trial offering “treatment” for OUD runs the risk of attracting a very small group of “treatment ready” individuals. Those willing to participate in a

traditional efficacy trial may also be those most motivated to address their substance use, potentially a much smaller subset of the broader group of patients presenting with these problems in everyday primary care practices.

The question this pragmatic trial seeks to answer is: "If we offer a CC service to patients with evidence of OUD and depression, what is the benefit among people to whom it's offered?" This CC program prioritizes patient-centered, non-stigmatized engagement and assessment of OUD recognition and readiness for OUD treatment, followed by shared decision making. An important element of this design is that the outreach must be more aligned with how patients would be approached, assessed, and engaged in clinical care, and then offered an opportunity to decide if the program interests them. This is a critical, because patients with a history of opioid related problems are often hard to engage and refining a clinical outreach process that is acceptable to patients and enhances engagement is a critical objective of the MI-CARE study.

2.2.2 IMPORTANCE OF AVOIDING ACTIVATION OF CONTROLS THROUGH STUDY RECRUITMENT AND ASSESSMENT

Paradoxical as it may seem, while many patients with OUD and other substance use are ambivalent about seeking and sustaining substance use-related treatment (and, hence, conventional trials likely selectively attract those most motivated for treatment), the softer nudge of outreach and self-assessment characteristic of an "assessment only" usual care study arm has been shown to motivate positive behavior change (reduced substance use) in substance use disorder studies. In the CHOICE trial of CC for alcohol use disorders,[29] patients reported being motivated to change their behavior based on information letters from their PCPs, recruitment outreach, and study assessments (which led them to think about their symptoms and reasons for change). Thus, recruitment could motivate the control arm, biasing the study to the null and missing the true impact of the CC program. In short, control arm patients outreached or administered study assessments are not experiencing true "usual care," and control patients could be activated to change their behavior.

2.2.3 BENEFITS OF ENCOURAGEMENT TRIAL DESIGN

Given the limitations of conventional trial designs described above, this study adopts an encouragement trial design such that all patients in participating healthcare systems who meet clinical eligibility criteria are enrolled in the study cohort and followed passively using secondary 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 CC program. The remaining 50% from the study cohort (not randomly selected to be offered the CC program) are thus the "usual care" comparison group and are never contacted by research staff, thereby eliminating the chance of activating behavior changes in the control arm due to study outreach, recruitment or assessments.

All those randomly selected to be offered the intervention—CC services—are included in the analysis, regardless of whether they are reached and choose to participate in the MI-CARE intervention or not.

This approach allows more flexibility in how and when a patient is engaged in the CC intervention, thereby potentially better representing patient-driven real-world care. The trial is patterned after CC as it would be offered in real-world practice. Consequently, a modified oral consent will be obtained at the time CC is offered to patients in the intervention arm. Some patients with documented OUD diagnoses may not recognize they have an OUD, or the diagnosis may have been placed in error, so our outreach initially focuses on depressive symptoms ("stress and low mood") and things that impact stress and low mood like pain, sleep, medications, or substance use.

To avoid the bias of getting only those willing to engage in research - outreach and the offer of CC are designed to mimic routine clinical care (while still fully informing CC arm patients they are participating in research), and outcomes data are collected entirely from electronic sources (e.g., EHR, claims data, prescription monitoring programs, and other clinical data bases) for all eligible and randomized patients.

3 OBJECTIVES AND OUTCOMES

3.1 OBJECTIVES

The MI-CARE trial evaluates the effectiveness of an offer of 12 months of CC to primary care patients with evidence of depression and OUD compared to usual primary care. The MI-CARE intervention is designed to support "whole health" by engaging patients in medication treatment for OUD and depression, reducing depressive symptoms, and addressing common comorbid conditions that complicate OUD and depression (e.g., anxiety, pain, sleep, and other mental health and substance use disorders).

3.2 MAIN OUTCOMES

Outcomes are evaluated in the total population-based cohort of primary care patients randomized for the trial based on documented depression symptoms and evidence of an OUD in the prior year in electronic data sources. All outcome measures are obtained from secondary health services information that can be obtained for the entire study cohort (e.g., EHR, claims, health information exchanges and State prescription monitoring programs). No primary data will be directly collected from participants for outcomes because 50% of patients are never contacted by the study.

3.2.1 PRIMARY TRIAL OUTCOME

AIM 1. Days of OUD medication treatment. A continuous measure of days of OUD treatment with buprenorphine in the 365 days after randomization.

Rationale: We use days of OUD treatment with buprenorphine as our main outcome to reflect both buprenorphine initiation and/or retention. Days of OUD medication treatment was recently selected and prioritized as the most important core outcome measure in a Core Outcome Set by a NIDA Clinical Trials Network Delphi process. We also include several secondary measures of OUD treatment. Although a consensus is emerging that days of OUD treatment is the optimal measure for OUD

treatment, these secondary measures will provide a fuller picture of treatment in our sample: days of any medication treatment for OUD, sustained buprenorphine treatment for OUD for 90 days,[30] buprenorphine treatment for OUD with 80% of days covered, and any OUD or other addiction treatment. We restrict to buprenorphine because it is the first line office-based treatment and therefore represents most office-based OUD treatment, and because injectable naltrexone and methadone treatment for OUD cannot be obtained consistently through the Health Information Exchange in Indiana.

We will obtain buprenorphine treatment data 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. These data sources have been used in prior studies, including the recent PROUD trial conducted by the NIDA CTN. At the same time, we recognize that patients in the MI-CARE usual care arm may be more likely to receive OUD treatment outside the healthcare system (in the absence of NCM support), which would be missed by these data systems, and could bias study outcomes. We therefore are making every effort to obtain more complete data from state prescription monitoring programs (PMPs) which are now available for research in both Indiana and Washington. State PMPs are the preferred data source because state level data provide the most unbiased source of our main outcome. However, because the process for PMP linkage is new to both sites, and state IRB applications require months, we cannot confirm feasibility at this time. If we obtain PMP data for the trial sample from both states, we will use it to measure the main outcome for the MI-CARE trial, as well as secondary outcomes based on buprenorphine or other opioids. If funding and time allow, we would also compare the main outcome measured with PMP data and the main outcome measured with EHR data, for a secondary paper to inform future pragmatic trials.

3.2.2 SECONDARY TRIAL OUTCOME - POWERED DEPRESSION OUTCOME

AIM 2: Improvement in depressive symptoms. A reduction in depressive symptoms from the study qualifying PHQ score to follow-up PHQ score documented as part of routine clinical care 3-13 months later.

The analytical approach to handling the situation in which some individuals have multiple PHQ measures documented during the follow-up window will be specified in the statistical analysis plan (a brief overview of the methods considered and the general simulation approach to guide the choice of method is given in Supplement 3, part B).

Rationale: A prior study found a change between 2.59 and 4.78 to be the minimal clinically important difference (MCID), leading to a commonly defined threshold of 3-5 points for the MCID. However, no studies have evaluated the PHQ in patients with OUD. Therefore, we chose to not pre-define a specified threshold. In addition, we use the interval of 3-13 months to ensure 60% follow-up PHQ-9s based on preliminary studies showing that 13 months after randomization maximizes follow-up (likely due to EHR prompts at 12 months for repeat screening). (See Supplement 2 for additional rationale).

To get a fuller picture of changes in depressive symptoms we will also assess clinically significant improvement in depressive symptoms defined as at least a 50% decrease in PHQ score.

3.2.3 SECONDARY TRIAL OUTCOMES TO SUPPORT FUTURE IMPLEMENTATION

AIM 3: Analyses to support future implementation. Formative evaluation and cost analyses are conducted to support future implementation.

3.2.3.1 FORMATIVE EVALUATION OUTCOMES

Formative evaluation includes both qualitative and quantitative components to support future implementation.

Qualitative elements of formative evaluation will identify barriers and facilitators to implementing the intervention in this pragmatic trial. Weekly debriefs of NCMs, with research staff observing and taking field notes on all meetings, will be used to surface important issues. These will be used to populate a virtual white board with sticky notes and then code barriers and facilitators into domains including: the external environment, such as changes in the opioid epidemic, or waivers needed to prescribe buprenorphine; the MI-CARE intervention, such as issues with engagement of patients and primary care providers and their teams, or changes in standard care; patients and the health systems, such as characteristics of eligible patients and primary care teams and others in the health systems; and implementation and sustainment infrastructure, related to how the intervention is integrated into each organization in a sustainable manner, as in building EHR tools for NCM use. Our NCM team will also conduct chart reviews of all MI-CARE enrollees (usual care, invited to CC but not consented and consented, to find information that is not readily identifiable through EHR data pull, specifically qualitative information that contextualizes our study variables (see Chart Abstraction form). In addition, the team will conduct qualitative interviews with all staff delivering the MI-CARE intervention (NCMs) and OBAT nurses supporting treatment to better understand their experiences with the training and support on the MI-CARE intervention at both sites. See Supplement 4 for additional information outlining this process.

Quantitative elements of formative evaluation will be based on RE-AIM model (Reach, Effectiveness, Adoption, Implementation fidelity and Maintenance). Reach, adoption and implementation fidelity will be evaluated. (Effectiveness is evaluated as above in main aims, and Maintenance after the trial is beyond the scope of this study).

- Reach of the Intervention. We will evaluate the overall reach at the patient level - namely, demographic and clinical characteristics of those consenting for treatment and engaging in care contrasted to those invited but failing to consent/engage in care. Further, we will evaluate uptake of core component elements at the patient level including: NCM engagement, use of

measurement-based care, recommendations made to primary care provider, buprenorphine treatment for OUD, buprenorphine for pain, behavioral activation, specialty addiction treatment, and change in depression treatment. Each will be evaluated in the full intervention sample and in subgroups based on demographic and clinical characteristics (e.g., prior buprenorphine treatment, serious mental illness, prescribed opioids at baseline).

- Adoption of the intervention by primary care providers. We will evaluate measures of adoption at the primary care provider or team level: (e.g., buprenorphine treatment for OUD, buprenorphine treatment for pain, and change in depressive treatment).
- Implementation fidelity will be evaluated at the level of the NCM and the site, and will include evidence of NCMs consistent use of the core components of CC interventions (as described in Section 6.4.1.) such as: use of measurement based care, communication and/or coordination with patients' primary care teams (and, as appropriate specialists providing care), recommendation of evidence-based care for OUD and depression, and associated mental health and substance use conditions; use of BA for OUD and depression, and associated mental health and substance use conditions and attention to patient-centered care (e.g., engagement, and attention to other patient-prioritized conditions and concerns as appropriate).

3.2.3.2 OUTCOMES ASSOCIATED WITH NURSE CARE MANAGER INTERVENTION DELIVERY EFFORTS

We have built a REDCap enabled data collection system for the trial that allows time tracking to classify and quantify NCM efforts to deliver the MICARE study intervention (which includes all required elements of CMS specifications for reimbursable Psychiatric Collaborative Care Model [CoCM] services). Nurses track both time spent in direct patient treatment as well as coordinating relevant clinical services on the patients' behalf. Outcomes to be tracked include (per patient):

- CMS Billable NCM time supporting MI-CARE (CoCM services). We will identify the NCM time with patients delivering MICARE services as well as providing care coordination that is reimbursable under current CMS allowable payment to non-physician practitioners and specified in CMS published CPT codes and billing parameters.
- Additional (nonbillable) NCM time engaged in MI-CARE intervention activities. We recognize that the clinical complexity and high burden of social determinants of health in the study population of patients serviced by MI-CARE may result in the NCM spending either more time in CoCM billable activities than reimbursable currently by CMS as well as in supporting patient needs that may fall outside of currently allowable CPT codes. We will track non-billable time as well as billable time, therefore, to better characterize NCM total effort needed to support patients with OUD, depression, and frequent concomitant conditions using the CoCM model.

Finally, although it is beyond the scope of what can be accomplished within the allowable timeframe of the funded project, we have data available to determine the total cost of delivery of the intervention and the EHR data to determine the cost of medical care in each group at baseline and over follow-up by

broad setting (e.g., inpatient, emergency, outpatient, pharmacy) as well as important categories (e.g., behavioral health, etc.) thus allowing the possibility for a separately funded future study to examine cost effectiveness. Using the framework of cost-effectiveness, this would also allow the estimation of the incremental cost per additional day of OUD treatment (as described in Section 3.2.1. above), our primary outcome in the study.

3.3 OTHER TRIAL OUTCOMES RELATED TO OUD, DEPRESSION, PAIN, AND ADVERSE OUTCOMES

3.3.1 OTHER SECONDARY TRIAL OUTCOMES

3.3.1.1 BUPRENORPHINE TREATMENT AND/OR IMPROVED DEPRESSIVE SYMPTOMS

This composite identifies patients prescribed any buprenorphine—for OUD or pain—and/or who have documentation of clinically-significant improvement in depressive symptoms, as defined in Section 3.2.2. This composite is the most inclusive measure of benefit for depression, OUD, or improved safety for pain management with medications.

- ***Treatment with buprenorphine*** is a binary measure of treatment with buprenorphine formulations for OUD or pain defined as > 90 days of buprenorphine during the 12-month follow up period.[3]
- ***Clinically significant improvement in depressive symptoms*** is a binary measure of documented clinical response of depressive symptoms during follow-up (50% decrease in PHQ9 score or negative PHQ2 screen).

Rationale: Our preliminary research (see Supplement 2) revealed that many eligible patients may not accept both components of the intervention focused on OUD and depression. Some may not have OUD despite the ICD diagnosis in their record (e.g., due to incorrect or imprecise diagnosis coding), while for others with serious mental illness, their index PHQ (e.g., score 11) may already reflect optimal management from specialty mental health providers. Further, some patients with chronic pain who are prescribed opioids and may not believe they have an OUD, could benefit from a switch from prescribed opioids to buprenorphine for pain. There is increasing evidence on the benefits of buprenorphine for chronic pain and evolving strategies for switching to buprenorphine from a full μ-opioid receptor agonist for chronic pain management.[31-33]

3.3.1.2 MAJOR ACUTE ADVERSE HEALTH EVENTS

A composite of any major adverse event over 12 months of follow-up, which includes: opioid overdose, other drug overdose, suicide attempt or other self-harm, hospitalizations (opioid and non-opioid), or death (from secondary data sources).

Rationale: This outcome assesses whether improved depressive symptoms and OUD and pain management has patient safety benefits.

3.3.1.3 SERIOUS OPIOID-RELATED EVENT

This is a count measure of the number of serious opioid-related emergency department (ED) visits or hospitalizations defined as any ED or hospital admission with a primary OUD or opioid-related diagnosis or an opioid-related overdose (lethal or non-lethal).[3]

Rationale: This outcome assesses whether improved management of depression, OUD and pain decreases dangerous opioid-related outcomes.

3.3.1.4 OTHER SECONDARY EXPLORATORY OUTCOMES

Due to the heterogeneity of the sample and the expected heterogeneity of benefits across different subsamples (e.g., heroin use vs prescribed opioids for pain as route to OUD), a number of secondary outcomes will be used to describe outcomes. Each individual component of secondary outcomes (e.g., buprenorphine for pain, suicide attempt, opioid overdose) will also be evaluated independently.

- ***Descriptive measures related to OUD*** will be assessed in both arms, including engagement in primary care for OUD and/or pain; other treatments for OUD (e.g., naltrexone, methadone from outpatient treatment programs (OTPs) as well as behavioral treatments inside or outside the health system such as counseling for SUD or addiction treatment programs, or inpatient addiction treatment), secondary prevention outcomes (e.g., urine drug screening including fentanyl, naloxone prescription for OD prevention, Hepatitis C virus (HCV) and HIV screening, absence of non-buprenorphine opioid and benzodiazepine prescribing); chances in treatment for OUD (e.g., initiation of new buprenorphine for OUD); days of buprenorphine pain treatment (e.g., Belbuca, Butrans, etc.); and other treatments for pain (e.g., specialty treatments for pain, other pain treatments, and new buprenorphine for pain).
- ***Depression measures*** assessed during follow-up (both arms) will include measures of measurement-based care, medication treatment, and counseling or behavioral treatments for depression of other mental health disorders (e.g., no follow-up PHQ score documented in the EHR; number of documented PHQs in follow-up, new or change in antidepressant medication or increase in antidepressant dose in 12 months follow-up; counseling for depression, inpatient psychiatric treatment, and suicidal thoughts on PHQ-9).
- ***Risk factors for adverse or improved outcomes*** will include urine drug screens with "unexpected" outcomes (e.g., lack of prescribed buprenorphine, opioids not prescribed, methamphetamine and other drugs, cannabis); prescribed opioids aside from buprenorphine; chronic prescription opioids at doses exceeding CDC established safety threshold of ≥ 50 morphine milligram equivalents per day (MED); prescription opioid use above lowest level safety threshold (≥ 20 MED)[34, 35]; prescribed benzodiazepines.
- ***Process measures of care assessing participation in the intervention*** (consenting intervention arm patients only) will include: NCM engagement (e.g., count of visits, duration of visits); documentation of care provided to intervention patients in the tracking REDCap database (e.g., receipt of behavioral activation intervention, safety planning, coordinating care, discussion with

other care providers), completion of patient-report measures for measurement-based care (e.g. PHQ, Opioid Use Monitor, etc); and results of all measurement-based care measures (e.g., PHQ-9, Opioid Use Monitor, GAD-7, etc).

3.3.2 COVARIATES

The sample will include important subgroups of patients who may respond differently to the intervention and for whom different outcomes are most relevant. Outcomes will therefore secondarily be described in important subgroups at baseline (defined as up to 2 years before randomization), including the following:

- ***Demographics of study population at baseline.*** Used to describe baseline characteristics of the sample (e.g., age, sex, race, ethnicity, zip code-based neighborhood characteristics such as SES and type of insurance).
- ***Diagnoses of medical conditions and clinical comorbidity at baseline.*** Used for stratified analyses and to explore whether these characteristics modify the reach or effectiveness of the intervention.
- ***Substance use-related and pain comorbidity at baseline***. Used for stratified analyses and to explore whether these characteristics modify the reach or effectiveness of the intervention.
- ***OUD medication treatment at baseline***. These groups will be used for stratified analyses, to explore whether these characteristics modify the reach or effectiveness of the intervention, and for subgroup analyses.
- ***Mental health subgroups at baseline***. We will evaluate sub-groups based on mental health comorbidity to explore whether the intervention has differential reach (engagement and OUD treatment) or effectiveness across subgroups (e.g., serious mental illness, ADHD, PTSD).
- ***Healthcare utilization at baseline*** (e.g., primary care, mental health, addiction specialty, ED, and hospital utilization, etc.). Used for stratified analyses and to explore whether these characteristics modify the reach or effectiveness of the intervention.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This encouragement trial uses a Zelen design. The Zelen design refers to identification of a cohort (step 1) and random assignment of patients to an intervention (step 2) before consent. In MI-CARE:

- ***STEP 1*** is to identify all eligible patients meeting OUD and depression criteria (“trial cohort”).
- ***STEP 2*** is to randomly select 50% of the eligible sample to be offered the MI-CARE CC intervention.

- ***STEP 3*** is to follow 100% of the trial cohort for 12 months using secondary data, comparing the 50% of patients randomly selected to be offered the intervention (irrespective of acceptance of the CC program) to all other patients in the trial cohort.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Patients are identified up to weekly using an adaptive schedule at each site based on the routine assessment of study nurses' availability. For example, new sample may not be identified some weeks due to nurse out-of-office schedules, or to allow nurses to catch up if a previous week resulted in a large influx of new patients. Data extraction from each site's EHR and data systems is used to identify a sample cohort that meets criteria below. Data extraction may take several days to run against health system databases. Samples are randomized the same day that data extraction is completed. The "index date", Day 0, is the date of randomization.

Eligible patients must meet all 4 of the criteria below:

(1) ≥1 in person or virtual encounter in a primary care setting in the 365 days prior to the data extraction start date at ≥1 primary care clinic.

(2) Age ≥18 years on or before the data extraction start date.

(3) ≥1 PHQ depression screening score of ≥10 in the 7 days prior to the data extraction start date.

(4) Evidence of OUD in the 365 days prior to and including the date of the qualifying PHQ-9 score. Any 1 of the following qualifies as evidence of OUD:

- ≥1 active OUD ICD-10 diagnosis code in any setting except labs and those covered by 42 CFR Part II (see Section 5.2, Exclusion Criteria for more about 42 CFR Part II);
- ≥1 prescription (orders or dispensed) for buprenorphine (oral formulations indicated for OUD, extended release injectable, and implant);
- ≥1 procedure code for buprenorphine (oral formulations indicated for OUD, extended release injectable, and implant);
- ≥1 ICD-10 codes for opioid overdose;
- ≥1 OUD ICD-10 code, including remission, and prescription (orders or dispensed) or procedure code for injectable naltrexone.

5.2 EXCLUSION CRITERIA

Patients are ineligible who meet any of the criteria below:

(1) The only indication of OUD or only PHQ available to determine eligibility came from data protected under 42 CFR Part 2 (e.g., insurance claims from 42 CFR Part 2 covered facilities; data

from an internal treatment program when data release for other internal care is not already documented in the EHR).

(2) The patient was randomized to the intervention arm of the pilot study and the NCM outreached the PCP and/or the patient for the pilot study OR was previously sampled and randomized for the pragmatic trial.

(3) Health system data indicate the patient required an English interpreter.

(4) Any one of the following conditions in the 2 years prior to and including the date of the qualifying PHQ:

- Alzheimer's disease or dementia diagnosis, or medication to treat Alzheimer's or dementia.
- Severe cognitive limitations.

(5) Current active treatment for cancer with chemotherapy or radiation therapy in the past 3 months (not including non-melanoma skin cancers).

(6) Previously requested to not participate in research;

(7) Documentation of hospice care in the 2 years prior to and including the date of the qualifying PHQ score;

(8) Patient actively being outreached for or is participating in depression care management (KPWA only)

6 STUDY PROCEDURES

6.1 ENROLLMENT PROCEDURES

6.1.1 IDENTIFICATION OF TRIAL COHORT USING ELECTRONIC DATA COLLECTION

The trial cohort of eligible patients will be identified by a local study programmer on up to a weekly basis from KPWA and IUH electronic health system data. All identified eligible patients are automatically (passively) enrolled. The sampling schedule will be adapted to nurse availability and workload (e.g., vacations, catching up on large influx of intervention arm patients in recent weeks).

6.1.1.1 ENROLLMENT DATA QUALITY CHECKING

It is possible for IUH's electronic data to have multiple medical record numbers (MRNs) assigned to an individual patient. A manual review will be conducted of all eligible patients prior to randomization to identify any duplicate identifiers, comparing each eligible patient to the list of patients outreached in the pilot (including outreach to PCP) or previously randomized. This review will be informed by a check of quantitative EHR data designed to highlight IUH EHR records that have duplicate identifiers to highlight patients needing special scrutiny (e.g., name, date of birth, address, phone) will be searched for matches

within the cohort identified for that week, and all previously randomized IUH patients (both arms) or patients outreached for the pilot. Confirmed duplicates will be excluded prior to randomization.

Our trial relies on computer code for identifying visits, diagnoses, and medications from EHR data to identify the trial sample. We will try to continually improve the precision of the code as needed, as there can be unintended subtleties. For example, we learned that our code for primary care encounters at IUH was identifying "registration" for primary care visits when no visit occurred. If future questions arise about similar anomalies in the EHR code, we will use chart review to explore. While nurse care managers can review the charts of intervention patients to understand the extent of an observed anomaly, we will sometimes need to also evaluate control patients or to briefly pause recruitment (and use one or more weeks of sample instead to explore a data anomaly) in order to improve the precision of our code for identifying the eligible sample.

6.1.2 RANDOM SELECTION OF SAMPLE OFFERED INTERVENTION (INTERVENTION GROUP)

Randomization lists for each site will be created by the study biostatistician prior to the start of the trial using a computer-generated list of random numbers. Patients will be randomized 1:1 to be offered the CC intervention in permuted blocks of size 4, 6, and 8 (to ensure approximately equal accrual into each arm of the study over time), and stratified by site (KPWA, IUH). Group assignment will be concealed by the computer program until eligible patients have been identified each week.

Day 0 is set as the randomization date. We note that data extraction may take several days to run against health system databases. Samples are randomized the same day that data extraction is completed.

6.1.3 USUAL CARE CONTROL ARM

Patients in the trial cohort who are not randomly selected to be offered the MI-CARE intervention are the Usual Care Control for comparison in trial analysis. The study has no contact with this usual care (observation only) group. This trial will not be contaminated by the pilot because we are excluding patients who had any outreach in the pilot. We do not expect contamination of the usual care arm because many implementation studies have shown how difficult it is to change primary care practice to address OUD without added support (such as the NCM in this study provides) to facilitate initiation of Buprenorphine, pharmacy orders for buprenorphine, and laboratory monitoring of patients on buprenorphine.

6.2 RECRUITMENT PROCEDURES FOR INTERVENTION GROUP

MI-CARE recruitment procedures reflect the purpose of the MI-CARE trial: to evaluate the effect of making a virtual CC program available as part of routine primary care to eligible patients. To achieve that purpose, several factors had to be considered, including the stigma associated with OUD and that providers could have documented an OUD diagnosis without the patient knowing about, or agreeing with, the OUD diagnosis. We conducted research activities to design a recruitment strategy that was

engaging to eligible patients, including telephone interviews and online surveys with eligible KPWA patients, and are conducting a pilot study. We also partnered with KPWA stakeholders with primary care expertise in OUD and mental health to design outreach procedures consistent with routine primary care.

Recruitment procedures are carefully designed to engage, but avoid offending, patients who did not consider that they had an OUD. As a result of this preliminary research and our experience to date in the pilot study, we have designed recruitment procedures with the following key elements:

- ***EHR review***. Prior to outreach and engagement, the NCM reviews each patient's chart to identify or confirm the PCP, and whether the patient is followed by mental health clinicians.
- ***Initial message to PCP***. The PCP is informed their patient is eligible for the program via an internal staff message in the EHR and invited 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 the patient does not have an established PCP, the designated PCP is no longer active in the health system, or it is clear the patient no longer sees the designated PCP, initial engagement with a PCP will not occur and the NCM will attempt initial contact with the patient directly. If the patient consents to the study, the NCM will offer to work with the patient to establish a PCP.
- ***Outreach to patients***. Outreach mimics the way CC would be initially offered to patients for depression. Patients with PHQ-9 ≥ 10 indicating moderate to severe depression are sent a brief message via the patient web portal and/or by mail. The communication allows patients to opt out before a call from the NCM. This initial message does not mention OUD given possible error in OUD diagnoses and stigma.
- ***Administering consent to patients***. Patients who do not opt out are phoned to obtain verbal consent. A written information sheet is sent to patients who consent via the patient's preferred method.

More information about each of these elements is provided in the following sub-sections.

6.2.1 INITIAL NCM ENGAGEMENT OF THE PCP

The procedures for engaging the PCP about potential study patients have been worked out in a manner that is optimal for clinical workflow. The NCM's initial contact with the PCP is by internal staff message. The PCP is informed the patient is eligible for the study, invited to send a personal outreach message to the patient about the program (at the PCP's preference), or to share information that might indicate that a patient should not currently be outreached (e.g., patient just entered a 28-day inpatient treatment program).

If a patient is well established with a mental health provider within the health care system, the NCM may also contact that clinician with information about the study and for care coordination based on the clinical scenario.

If the patient does not have an established PCP, the designated PCP is no longer active in the health system, or it is clear the patient no longer sees the designated PCP, initial engagement with a PCP will not occur and the NCM sill send the initial message directly to the patient. If the patient consents to be in the study, the NCM will offer to work with the patient to establish a PCP.

6.2.2 NCM SENDS INVITATION TO INTERVENTION GROUP PATIENTS

Following PCP outreach (if applicable), the NCM sends all patients not opted out by their PCP a communication (e.g., via patient web portal message, pre-verified personal email, or mailed letter). This communication lets the patient know the NCM will be reaching out by phone about a primary care program supported by research that is available to them and offers study contact information (e.g., contact card with NCM work cell phone number, study email) for patients to contact to opt out or reach out to with questions. The communication will also include information about the possibility of the study team providing the participant with a free cell phone or cell phone minutes if needed. Two days are allowed for the patient to review and respond to the message using their preferred mode of communication (call, text, email, patient web portal reply). Four days are allowed if the invitation was sent as a mailed letter.

6.3 ADMINISTRATION OF MODIFIED INFORMED CONSENT

The NCM will call patients who have not opted out. Outreach and verbal consent will mimic 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 care as usual, patients can stop participating in CC at any time).

An IRB-approved telephone script for a modified verbal consent procedure will be used to describe the study and MI-CARE program, provide elements of informed consent, and invite patients to ask questions. Oral consent (Y/N) and the date of oral consent will be documented in the study database by the NCM.

Consenting patients are sent a study information sheet and wallet-sized study contact card after the consent call.

6.4 MI-CARE COLLABORATIVE CARE INTERVENTION

6.4.1 BACKGROUND

The Collaborative Care Model was originally designed to improve mental health outcomes in primary care and includes 5 essential elements.[36] The CC intervention tested in the MI-CARE trial will include each of these elements.

1) ***Population-based Care***. All eligible patients are managed proactively using a study patient registry so that patients don't "fall through the cracks" of primary care. Specifically, in MI-CARE the NCM provides outreach to eligible patients with depressive symptoms and OUD

documented in the EHR, using motivational interviewing to engage consented patients, and providing proactive follow-up based on the MI-CARE patient registry, which is reviewed weekly with expert consultants.

2) ***Patient-centered Team Care***. The NCM and a primary care team work together to provide patient-centered care. Specifically, the NCM uses 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. The NCM routinely communicates patient preferences and choices, as well as expert consultant recommendations, to the primary care team and other care providers, as appropriate to support the delivery of care.

3) ***Evidence-based Care***. The NCM supports evidence-based psychosocial and pharmacologic treatments. Specifically, in MI-CARE the NCM is supported weekly by expert consultation providing recommendations for specific patients, and the NCM communicates recommendations to the primary care team. The NCM also supports patients in accessing selected evidence-based treatments from the primary care team or outside providers (e.g., medication treatment for OUD, medication or counseling for depression) and offers behavioral activation, as appropriate.

4) ***Measurement-based Treatment to Target***. The NCM uses systematic clinical outcomes measures to support treatment and treatment adjustments. Specifically, the NCM introduces systematic measures (e.g., PHQ for depression, measure(s) to assess OUD symptoms) when engaging with consented patients. Patient reported outcome measures are then used to monitor symptoms of OUD, depression and other conditions per patient preference, over time.[36,37 38-41]

5) ***Accountable Care***. The NCM, the expert consultants, and primary care team are responsible for individual patients and the population of patients. Specifically, the NCM and consultants will review the MI-CARE patient registry weekly throughout the follow-up period and identify approaches to improving the quality of care.

The MI-CARE intervention will be administered by a nurse care manager over the phone or video. Video visits may be used, upon patient preference, after any barriers have been addressed (e.g., reliability of internet access, patient privacy concerns, device compatibility, local health system telehealth policies).

Medical treatment is provided by licensed physicians and providers in the participating health systems. While the NCMs offer motivational interviewing and may engage patients in behavioral activation, they and the MI-CARE expert consultants play a supportive role. The NCM role, expert consultants, and systems of care (e.g., measurement-based care measures, MI-CARE patient registry) are all designed to support patients and primary care teams virtually. Primary care teams see patients for in-person or virtual visits (telephone and video), order medications, refer patients to care, and provide clinical care for OUD and depressive symptoms.

6.4.2 STUDY INTERVENTION PROCEDURES

6.4.2.1 SYSTEMATIC CLINICAL ASSESSMENTS TO SUPPORT MEASUREMENT-BASED CARE

When oral consent is obtained, the NCM will obtain and verify a personal email address and cell phone number for each participant. The email address will be used by the NCM throughout the program period to send participants links to online clinical assessments for depression, OUD and other conditions to monitor symptoms and progress toward goals. The assessments are collected using the secure online survey platform REDCap; some scored assessments (e.g., PHQ-9 scores) will be documented in text notes of NCM phone encounters in the EHR. If email is a barrier for a patient, a link may be sent to the verified cell number (if a smartphone). The NCM may also administer assessments to patients by phone.

- ***Baseline clinical assessments*** will typically include the PHQ-9; symptoms of OUD, and other substance use including tobacco and alcohol, but may be tailored (e.g. to decrease burden in patients who are unable to complete all). Brief screens for other common conditions may also be collected at baseline (chronic pain, anxiety, psychosis and mania, PTSD). A positive screen for recent thoughts of suicide (item 9 of PHQ-9) will trigger a standard secondary clinical assessment for suicide risk.
- ***Ongoing clinical assessments*** to support measurement-based care will be tailored, as appropriate, to the specific participant and may include core PHQ and OUD measures along with other measures (e.g., pain, sleep, anxiety, alcohol use, other drug use)
- ***Assessment of patient experience of the CC program***. Online REDCap questions about overall satisfaction with the MI-CARE program will be added to the assessment at the end of the 12-month period. NCMs may also periodically elicit feedback from participating patients on their experience and how the study CC program could be improved.

6.4.2.2 PROGRAM ENGAGEMENT

The MI-CARE program begins with NCM care focused on PCP and patient engagement.

- ***Care team engagement***. In addition to engaging the patient, the engagement process is designed to build the relationship between the NCM and the primary care team. Prior to a patient's first outreach call, the NCM informs the PCP that their patient was selected for the CC program and offers to have an initial brief (optional) call about the program with the care team. The NCM may also reach out to engage with specialty mental health providers who are working closely with the patient. If the patient does not have an established PCP, the NCM will offer to work with the patient to establish a PCP within the healthcare system. Additionally, each site's collaborative care consultants will message PCPs in their health plan when a given PCP's patient consents to participate in the MICARE intervention. These messages are to inform the PCP of the support the CC consultants provide each NCM in the management of consented patients to the

intervention (including that the CC consultant's role may include various recommendations regarding patient care).

- ***Patient engagement***. This begins with a short series of "engagement" sessions to develop a relationship with the patient. Engagement sessions focus on eliciting a patient's health narrative, including current symptoms, and exploring the patient's (general) health goals, priorities, and preferences. Prior to the first engagement call the NCM reviews the patient's chart to obtain current treatment(s) for depression, OUD and related conditions. The NCM will build rapport by learning about patients' lives, how they are impacted by their health, eliciting the patients' thoughts on symptoms reported, and exploring how the program might help them. Motivational interviewing and shared decision-making techniques are used to elicit patient goals and priorities.

Beginning with engagement and throughout the follow up period, the NCM will use common elements of two evidence-based core behavioral approaches:

- ***Motivational interviewing*** (MI) skills to elicit ambivalence and move patients toward wanting to improve OUD, depression or other related conditions; and
- ***Behavioral activation*** (BA) to help participants build skills to increase positive adaptive experiences in their day-to-day lives and support broader treatment gains.

To support NCMs in improving clinical MI and BA skills, NCM visits are audio-recorded with patient permission for ongoing supervision and quality purposes. Participants are informed by both verbal consent and in the Study Information Sheet about audio-recording visits for quality purposes and that they are free to request at any time that MI-CARE call(s) not be audio-recorded and still receive intervention calls. Consent to audio-recordings is not a requirement for participation in the MI-CARE program.

6.4.2.3 PROACTIVELY SCHEDULED PARTICIPANT FOLLOW UP

NCMs proactively schedule follow-up telephone sessions with participants. The recommended schedule of visits is outlined below but visit frequency will be tailored to patient clinical needs and preferences. The frequency will increase for unstable patients or those initiating buprenorphine. Some patients will request less frequent visits, and many will miss scheduled visits, resulting in less frequent visits.

- 2 times/week for first week
- Weekly calls for weeks ~2 – 12
- Biweekly to monthly calls for weeks 13 – 20
- Monthly, as needed for weeks 20 – 52

Deviations from this proactive call schedule (e.g., more frequent or less frequent calls, pausing of the intervention, increasing intensity due to relapse) may occur for many reasons. These are not considered

departures from the protocol due to the pragmatic nature of the study. See Section 11.2.3, Events Not Considered Protocol Divergences.

The total length of each participant's study period is not adjusted by pauses (index date + 365 days).

6.4.2.4 WEEKLY REVIEW WITH CC CONSULTANTS

The team of expert consultants will include a supervising psychiatrist and/or PCP with expertise in addiction medicine from KPWA and from IUH. Most weekly CC meetings (and/or in separate NCM sessions) will include a nurse expert in managing OUD from Boston Medical Center, where the Massachusetts Model for office-based CC for OUD was developed. The PIs and clinician-investigators (physicians and psychologists) may also participate in CC discussions. In addition, interdisciplinary team members may observe weekly review sessions (e.g., psychologist providing MI/BA supervision, observers to monitor/ensure consistency in approach). Once patients are consented to the intervention, the CC consultants will outreach the PCP to let them know about their role in providing recommendations and support to the NCMs in their respective health delivery system.

The NCM will provide a structured overview of newly engaged CC patients and share the patient's history, results of screenings and assessments, patient preferences, and other information that may be useful to developing a patient-centered treatment plan. CC consultants from the NCM's health system will provide recommendations on management of depressive symptoms and OUD, as well as issues that complicate these conditions including, but not limited to: anxiety, other mental health disorders, substance use, other substance use disorders, pain, and sleep disturbances. CC consultants will sometimes make specific recommendations to the primary care team, which NCMs will document in the patient's EHR and alert relevant providers.

Each NCM will discuss all their new patients and any unstable patients with CC expert consultants weekly. In addition, CC expert consultants will use the registry to review the NCM's panel of participants (ensuring that even stable patients are discussed at least monthly). The MI-CARE patient registry will display the most recent OUD and depression symptom measures for all consenting patients who remain in their active 12-month windows. CC consultations will focus particularly on patients who are not engaging in, tolerating or responding to treatment; and unstable patients (i.e., active substance use or suicidality). CC expert consultants may recommend modifications to such participants' treatment plans. The NCM documents and communicates care recommendations to the PCP and primary care team via the EHR, augmented by telephone contact or staff messaging if needed.

6.4.2.5 NCM COMMUNICATION WITH PCP AND PRIMARY CARE TEAM

NCMs work centrally, yet team up with primary care providers across the health system (> 30 KPWA clinics, >50 IUH clinics). Initial PCP outreach is detailed in section 6.2.1. Subsequent, ongoing outreach by the NCM to the primary care team will be primarily via the EHR (e.g., EHR progress notes from phone visits), via staff messages and occasional phone calls. The NCM will convey CC expert consultation recommendations for treatment plans and adjustments to the PCP and primary care team via these

same approaches. The NCM may also include other clinicians who are actively involved in patients' care (e.g., pain specialists, mental health providers) on messages to the care team, as clinically appropriate.

6.4.2.6 INITIATING AND OPTIMIZING USE OF MEDICATIONS TO TREAT OUD

A high priority of the NCM is to support those with OUD in accessing effective, evidence-based medication treatment for OUD. Treatment of OUD will generally take precedence over other concerns; however, patient preferences and safety will always inform the priority.

The NCM's role will support standard medication treatments of OUD in primary care, as well as self-management by the patient. If patients are willing, the NCM will support them in starting medication treatment of OUD. Treatment will usually be initiated at home with telephone support from the NCM per usual practice. Some patients may have taken medications to treat OUD previously or have already initiated treatment. The NCM will support these participants in reinitiating or optimizing the use of medications to treat OUD, in coordination with the primary care team.

Medications to treat OUD in primary care include buprenorphine and injectable or implantable naltrexone. Buprenorphine is the first line treatment for OUD in primary care. Injectable extended-release naltrexone is also an effective treatment but is second line because it requires a period of abstinence which can be difficult to achieve for some primary care patients with OUD.

Methadone cannot be prescribed for OUD in primary care and therefore will not be initiated as a primary care treatment option as a component of this study. However, the NCM could support a patient's engagement and/or retention in an external outpatient methadone treatment program.

6.4.2.7 SUPPORTING MEDICATION MANAGEMENT

MI-CARE participants and their primary care teams may start or change doses of medications for OUD, depression or other commonly co-occurring conditions, choose not to start medications, opt to re-start medications after a lapse, or may already be using such medications at the time of enrollment. Medication management support by the NCM will reinforce adherence, self-management skills by the patient, and identify any barriers to sustaining medication treatment plans.

The NCM will support medication management for OUD by reaching out to participants at least weekly during periods of initiation, re-initiation, or dose change. NCM support will include monitoring whether the medication prescription was filled, checking in on side effects and adherence, assessing changes in OUD symptoms (e.g., craving) via clinical assessments/measures, and monitoring urine drug screens (if being used by the primary care team).

NCMs will share information with the CC expert consultants and with the PCP. Modifications to the treatment plan may be suggested by the CC expert consultants if a participant is not tolerating or adhering to the medication or relapses to illicit opioids.

The NCM will similarly support the management of medications for depression and other conditions (e.g., anxiety, sleep, pain) prescribed by the PCP. This will include re-evaluating the effectiveness of medications for depression based on the PHQ and other assessment scores and monitoring adherence and side effects.

6.4.2.8 SUPPORTING REFERRALS TO OTHER BEHAVIORAL HEALTH RESOURCES

PCPs may order referrals to mental health specialty care (e.g., psychiatry, counseling, external methadone treatment). As appropriate, the NCM will assist the patient in connecting with these services, support the patient in staying engaged with such services during the study period, and provide clinically relevant updates to the PCP and other providers in the EHR.

PCPs may also connect patients to other internal services available in the health system (e.g., social workers, community resource specialists). NCMs will also help coordinate such services, if needed.

NCMs will also support patient involvement in other recovery supports (e.g., Narcotics Anonymous and other peer support or community groups).

6.4.2.9 UNCOMMON INSTANCES WHEN MI-CARE PARTICIPANTS ARE JUSTICE INVOLVED

In the uncommon (but anticipated) occurrence that MI-CARE participants become or disclose involvement with the justice system, the NCMs will follow normal health system procedures for their care. Specifically, if patients are incarcerated, under house arrest, or on parole, the NCMs will continue to support them, whenever possible. Support in these instances could include (but is not limited to): coordination of care, communicating patients' medication lists to corrections departments, supporting patients by phone (if possible and patient desires), and supporting transitions out of incarceration (a high-risk period with increased mortality). NCMs will have patients sign standard health system release of information forms, as needed.

6.5 INTERVENTION INTEGRITY

6.5.1 NURSE CARE MANAGER TRAINING

Initial NCM training consists of approximately 6.5 days on main components outlined in the subsections that follow.

6.5.1.1 MEDICATION MANAGEMENT OF OUD

Two half-day orientations to the Massachusetts Model of medication for OUD treatment. This training will include didactics and the sharing of experienced NCMs offering office-based addiction treatment.

6.5.1.2 COLLABORATIVE CARE, MEASUREMENT-BASED CARE, AND MEDICATION MANAGEMENT

Two half-days of training in CC for depression medications, measurement-based care for depression and OUD, and medication management. This will blend standard CC for depression with medication

management for OUD, use of symptoms in clinical care, use of the MI-CARE registry, presenting patients efficiently to the CC team (developed with role plays), and communicating with PCPs.

6.5.1.3 CRISIS PROTOCOLS, PLANNING AND RELATED WORKFLOWS

An additional half day of training for protocols for patients with suicidal thoughts, including chronic suicidal ideation, creation and documenting of crisis plans, and coordination/communication with primary care teams and others in the health care system are provided to nurses.

6.5.1.4 BEHAVIORAL ACTIVATION AND MOTIVATIONAL INTERVIEWING TECHNIQUES

Foundational training on behavioral activation and motivational interviewing techniques will be provided (at least 8 hours). This trains NCMs on core skills and strategies for how best to weave these into the overall CC treatment approach.

6.5.2 SUPERVISION BY A PSYCHOLOGIST

Psychologists will meet with NCMs weekly early in the trial and regularly thereafter to provide feedback and ongoing training on the motivational interviewing and behavioral activation skills. These sessions are based on the psychologist's review of audio-recorded MI-CARE CC sessions. These sessions will be used as necessary to ensure MI and BA skills are maintained and improved, and to prevent drift. These sessions provide clinical supervision and support to NCMs in utilizing and integrating motivational interviewing and behavioral activation approaches into the broader CC intervention.

Each health system will securely transfer a sampling of NCM audio recordings of sessions regularly to supervising psychologists at the University of Washington, the University of New Mexico, KP Washington, KP Northwest, and Montana State University for such review.

6.5.3 PEER NURSING SUPPORT FOR NURSE CARE MANAGEMENT OF OUD

NCMs will have access to national nurse experts in office-based CC for OUD treatment from Boston University for ad-hoc phone or email consultation. Nurse experts will also meet weekly with NCMs to support their work with MICARE patients.

A peer with a deep understanding of the inherent challenges of this clinical work and extensive experience working with patients with OUD and their primary care providers and teams will be an important source of support for NCMs delivering the MI-CARE intervention. The expert nurses' will provide suggestions to study NCMs about engaging patients and supporting their care needs based on their significant experience.

6.6 DISENGAGEMENT, RE-ENGAGEMENT AND "OPTING OUT" OF INTERVENTION

MI-CARE is an encouragement trial designed to evaluate the impact of offering the CC intervention to a population of patients with OUD and depression, and engagement with the NCM is a secondary outcome evaluated as an exploratory mediator. Therefore, the MI-CARE CC program is offered the way

it would be offered in actual practice, that is, with patients able to choose to disengage at any time (e.g., after a few sessions, to 'try it out'), and to re-engage again when and if they want during the 12-month intervention period, should they so choose. The NCM makes it clear to patients that MI-CARE is a research program.

Study staff will track patients who request to opt out of or discontinue the intervention in the study database. These patients may be sent a courtesy mailing with nurse contact card and a reminder of the end date of their intervention period.

6.6.1 COMMUNICATION WITH PCP PRIOR TO RECRUITMENT CALL

The NCM's communication with the PCP about potential study patients will be by internal staff message through the EHR., as described in Section 6.4.2.5.

6.6.2 COMMUNICATION WITH PATIENT PRIOR TO RECRUITMENT CALL

Following PCP outreach, potential CC participants are sent a patient web portal message, letter, or email to a pre-verified address to introduce the study per local health care system guidelines. This communication includes the NCM's cell phone number, a study voicemail number, and a study email address (e.g., contact card). Patients may proactively outreach the study to opt out of NCM recruitment calls via their preferred mode (e.g., phone, text, email, or web portal reply message).

- ***Patients proactively opting out prior to the recruitment call***. Ambivalence is a common element of OUD. A program offering CC for OUD or depression in practice would make it easy for patients to access support later, when desired. Therefore, patients opting out prior to NCM outreach will be informed, by either reply message and/or mail, that they can still access the program if they change their mind over the next year. Contact information for the study and NCM will be provided via a contact card when a mailing is sent.
- ***Patients never successfully reached for a recruitment call***. Some eligible patients will be extremely difficult to reach due to housing instability and other factors. NCMs will continue to outreach patients using the same modes used clinically (e.g., mail, web portal, text) who cannot be contacted, but in a tapered manner post-randomization. Follow up mailings including the nurse contact card may be sent when phone contact has not been successful. As housing instability may be an issue, NCMs will follow standard clinical practices at their respective health system to update patient contact information. This would include the NCM periodically re-reviewing the patient chart for updated contact information, and for indications of the patient's current status (e.g., homelessness, incarceration, receiving inpatient treatment, relocation, death).

6.6.3 PATIENT OPPORTUNITY TO DECLINE THE INTERVENTION DURING RECRUITMENT CALL

Patients who have not opted-out of recruitment within 2 days of study staff sending an electronic introductory message, or within 4 days of mailing a letter, are phoned by the NCM. Patients are free to

decline the offer of the CC program. As noted, ambivalence is a common element of OUD and this study is designed to mimic the approach that would be taken in everyday clinical practice. Therefore, (a) the NCM will inform patients by phone that they are eligible for the MI-CARE program for 12 months, asked for permission to call back in a few weeks or months and offered the NCM's cell phone number and, (b) one or more reminders of CC program offer may be sent during their 12-month period.

Those who choose to decline the offer of CC may be asked about services for low mood, worry, stress, pain, opioid use, or sleep that might be of interest, prior to ending the phone call. This may help us better understand barriers and improve patient acceptability of the intervention over time.

6.6.4 LOSS OF CONTACT FOLLOWING CONSENT

The NCM may lose contact with a patient who previously consented for many reasons (e.g., relapse, death, housing or financial instability, loss of phone access). During CC engagement, the NCM may ask the patient for additional contact person(s) or means through which to communicate with the patient, should contact be lost. If the NCM is concerned for the patient's safety (e.g., recent overdose or relapse), the emergency contact in the EHR may be contacted, per care standards.

The NCM will also utilize approaches described in Section 6.6.2 for patients never able to be reached (e.g., call attempts spread across days and times, voice messages, mail and/or web portal communications, EHR review) and may also message a study- or health system-verified email address or cell number, in keeping with the health system's standard practices.

The NCM will continue outreach in a tapered manner. Patients remain eligible for NCM support over the full 12-month period, should they choose to reach out.

6.6.5 DISCONTINUING THE INTERVENTION AFTER CONSENT

Participants who consent to the intervention can temporarily or permanently discontinue participation in the intervention at any time by calling or texting the NCM directly or messaging the study email or voicemail.

Participants temporarily discontinuing will be outreached by the NCM after an agreed upon period. Permanently discontinuing patients will be reminded that they may opt back in at any time during their remaining 12-month window and the NCM may offer to check back with them later (e.g., in a month or two) to see if it is a better time for them. A mailing with the nurse contact card and a reminder of their intervention window end date may be sent.

7 RISK/BENEFIT ASSESSMENT

7.1 KNOWN POTENTIAL RISKS

The known potential for risk to participants include typical clinical risks (e.g., discomfort answering questions about opioid use, side effects from medications prescribed by their care team), as well as study-specific risks. This pragmatic trial aligns with usual care and nurses are working directly in the health systems in partnership with the care team and charting in the patient medical record. Therefore, we focus here on known study risks, which include:

- Accidental disclosure of protected health information (both study arms);
- Risks due to accidental disclosure of participation in a 42 CFR Part II covered substance use disorders treatment program may exist for some patients (intervention participants only).

7.2 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risks of being offered and participating in the CC program are considered minimal, especially compared to the risks of inadequately treated OUD and/or depression. The CC program is intended to facilitate the delivery of empirically supported treatment in coordination with existing care providers. Treating providers will make all final decisions regarding prescription of specific treatments or referrals for specialty care. All members of the study cohort who do not agree to participate in the CC program or who are randomized to usual care (observation only) will continue to receive usual care, which in turn will neither increase risk nor deprive those individuals of any evaluation or treatment that would have occurred prior to or outside of the proposed trial. Further, no treatments are withheld or delayed in either arm. The health system already offers access to mental health services, medications for OUD, and other types of care management and study participants in both arms are free to seek and receive any services normally available to them.

While we hope that offering the MI-CARE CC program will increase engagement in life-saving OUD treatment, reduce symptoms of depression, and reduce risk of adverse outcomes (e.g., overdose, hospitalization, death), we have no evidence for effectiveness at this time. These are the primary study questions we are seeking to answer with the trial. That said, the potential importance of the knowledge to be gained is substantial as the proposed research provides an opportunity to dramatically improve access to care for OUD and depression and co-occurring related conditions. As such, we would suggest any risks inherent in conducting this research (see Sections 7.1 and 7.2, above) are justified by the potential larger benefits of the study and the steps we have taken to mitigate risks for participants in the study. See also Section 12 below (Ethics/Protection of Human Subjects) and Supplement 1, justifying the trial as minimal risks for the waivers needed to conduct a Zelen design trial, described in the next section. Note that waivers of consent, documentation of consent, and HIPAA Authorization were approved by the IRB in September 2020.

7.3 WAIVERS TO CONDUCT ENCOURAGEMENT TRIALS/ZELEN DESIGN

Detailed justifications and rationale for all required waivers to conduct the pilot study and pre-trial activities were provided to the IRB in a Supplement submitted when a pilot/trial protocol was initially reviewed and approved in September 2020. Waivers were granted to:

- Screen and identify eligible sample for randomization using existing health system databases (pilot and trial);
- Conduct pre-consent chart reviews and PCP outreach with MI-CARE arm patients (pilot and trial);
- Administer modified, oral consent to those offered the CC intervention (pilot and trial); and
- Collect secondary data to follow the entire study cohort for outcome, secondary, and covariate analyses (trial only). Of note, patients offered the CC intervention are included in the trial analyses even if they "opt out" or decline the CC intervention or cannot be reached.

Supplement 1 to this protocol provided updated rationale and justification for these waivers for the trial and for waivers needed to conduct secondary, data-only analyses using retrospective data to verify the programming code used in the trial to identify the sample, write computer programs to clean, code, and analyze all outcomes and covariates, to allow rapid trial analyses, due to the end of HEAL funding May 2024 and delays due to COVID.

8 STATISTICAL CONSIDERATIONS

8.1 SAMPLE SIZE DETERMINATION

Patients are eligible for the trial if they meet eligibility criteria in the EHR, have a recent elevated PHQ score and evidence of OUD in the last year. We will enroll at least 800 patients across the 2 health systems. Based on preliminary analysis of recent rates of patients with OUD diagnoses with qualifying PHQ scores at KPWA and IUH we expect between 800-900 patients will be enrolled in a 12-month period.

8.1.1 AIM 1 (PRIMARY) OUTCOME POWER

With a sample size of 760 patients (assuming 5% of the target 800 are missing outcome data, e.g., due to leaving the state) we will have 80% power to detect a difference in the mean number of days of OUD treatment (primary outcome) of 20 days under a two-sided type 1 error rate of 0.05, assuming a standard deviation (SD) of 98.3 (based on preliminary data). Because we expect that half or more of patients randomized to the trial intervention arm will not agree to participate in the intervention, this incremental benefit 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); see **Table 8.1.1**. For example, if 35% of patients engage with the intervention, to have 80% power we would need to observe a mean difference of 57.1 days of OUD treatment comparing engaged patients versus usual care patients (e.g., from 46.7 to 103.8 days), whereas if 50% engage we would need to observe a mean difference of 40 days (from 46.7 to 86.7 days). In these calculations, information on the mean and SD of the outcome was estimated using preliminary data from one of the two sites (the other site did not have preliminary data available on the primary outcome at the time of Protocol development).

Table 8.1.1. Minimal detectable difference (MDD) in the mean number of days of OUD treatment with 80% power comparing intervention versus control patients (intention-to-treat [ITT] analysis); and corresponding difference among engaged patients, across levels of engagement from 30-50%. MDDs are presented under different values of the R^2 of the included baseline covariates (e.g., baseline value of the outcome).

R^2 of baseline covariate	**Mean change in days of OUD treatment**					
	ITT	**Engaged patients (%) versus usual care**				
		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

Under our planned analysis that adjusts for the baseline value of the outcome (and potentially other covariates associated with the outcome; see Section 8.3) we will be able to observe smaller incremental benefits. For example, for a moderately prognostic covariate (R^2 of 0.20) we will be able to detect a mean change of 17.9 days among intervention patients (51.1 days among engaged patients if 35% engage), and for more highly prognostic covariate (R^2 of 0.40) we will be able to detect a mean change of 15.5 days among intervention patients (44.3 days among engaged patients if 35% engage).

Minimal detectable differences (MDDs) presented in the Table 8.1.1 are based on a linear regression for a normally distributed outcome. Although our outcome is non-normally distributed (range from 0 to 365 days with a peak at 0 days and a smaller peak at 365 days), Monte Carlo simulations that generated outcome data from a beta distribution, which well approximated the observed outcome distribution, indicated that a normal approximation performs well in estimating power given our relatively large sample size (details in Supplement 3, part A).

8.1.2 AIM 2 (SECONDARY) OUTCOME POWER

AIM 2: Improvement in depressive symptoms. Our Aim 2 outcome is a reduction in depressive symptoms from the study qualifying PHQ score to follow-up PHQ score documented as part of routine clinical care 3-13 months later.

Power calculations for Aim 2 estimate Minimal detectable difference (MDDs) that could be observed with 80% power, assuming a two-sided type 1 error rate of 0.05, under different scenarios regarding engagement (ranging from 30-50%). These calculations assume a 60% PHQ follow-up rate (among the initial sample of 800 patients) and standard deviation of 6.7 for the outcome, based on preliminary data from both study sites. Similar to Aim 1, the analysis for Aim 2 will adjust for the baseline value of the outcome (and potentially other baseline covariates). MDDs are also computed for a range of R^2 related to these prognostic variables, ranging from R^2 of 0 (corresponding to no prognostic covariates) to 0.4 (corresponding to more highly prognostic covariates). For engagement rates of at least 35%, or for lower engagement rates combined with highly prognostic baseline characteristics, the study sample size of 800 has sufficient power to detect a clinically meaningful difference of at least 5 for the outcome of change in PHQ, between baseline and intervention patients (and smaller in some scenarios). A prior study found a change between 2.59-4.78 to be the minimal clinically important difference (MCID), leading to a commonly defined threshold of 3-5 points for the MCID.

Table 8.1.2. Minimal detectable difference (MDD) in change in PHQ score, from baseline to follow-up, with 80% power comparing intervention versus control patients (intention-to-treat [ITT] analysis); and corresponding difference among engaged patients, across levels of engagement from 30-50%. MDDs are presented under different values of the R^2 of the included baseline covariates (e.g., baseline value of the outcome).

R^2 of baseline covariate	**Mean change in in PHQ score, from baseline to follow-up**					
	ITT	**Engaged patients (%) versus usual care**				
		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

8.2 POPULATIONS FOR ANALYSIS

Main analyses will be conducted following an intention-to-treat approach, including all individuals randomly selected to be offered the intervention (regardless of their engagement with or exposure to the intervention), as well as all patients not randomly selected to be offered the intervention (usual care controls), under the Zelen design.

8.3 STATISTICAL ANALYSES

8.3.1 ANALYSIS OF THE PRIMARY OUTCOME

The primary outcome is a continuous measure of days of OUD treatment with buprenorphine in the 365 days after randomization. We will use a linear regression analysis adjusted for the baseline value of the outcome, health system, and other pre-specified covariates measured pre-randomization (i.e., analysis of covariance [ANCOVA]). From the regression model we will estimate the mean difference in days of OUD treatment comparing patients randomly selected to be offered the CC intervention vs. the usual primary care control arm. Standard errors will be calculated using the robust (sandwich) variance estimator[42] given the non-normally distributed outcome (see Supplement 3, part A). Unless otherwise specified, all analyses will follow intention-to-treat principles with individuals analyzed according to the randomized intervention group.

Adjusting for baseline variables associated with the outcome can improve precision of intervention effect estimates and power of statistical tests.[43, 44] To determine the set of baseline variables that will be

adjusted for (in addition to health system and the baseline value of the outcome), we plan to use secondary data from before the start of the trial to conduct simulations to identify which covariates are associated with days of OUD treatment (measured in preliminary data) and to explore the impact of adjustment for such covariates on precision and power.[45] We reiterate that no post-randomization data will be used for covariate selection. The full details of the simulation-based approach and the variables selected for adjustment in the primary analysis will be pre-specified in the standalone statistical analysis plan (SAP) for the trial.

8.3.2 ANALYSIS OF THE SECONDARY DEPRESSIVE SYMPTOM OUTCOME

The powered secondary outcome is the change in PHQ score from baseline to follow-up (in the period 3-13 months after randomization). Following a similar approach as for the primary outcome, we will use a linear regression analysis of the change score (follow-up score minus baseline score), adjusted for the baseline score, health system, 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 selected to be offered the CC intervention vs. the usual primary care control arm. Standard errors will be calculated using the robust (sandwich) variance estimator. The set of baseline variables that will be adjusted for will be selected using a parallel approach as for the primary outcome, pre-specified in the standalone SAP.

Based on preliminary data, we expect that a subset of patients will have more than one follow-up PHQ (either PHQ-2 or PHQ-9) documented within the follow-up window. To determine our final approach to identifying which of these follow-up scores will be used, our biostatistical team will be conducting simulations to identify the most powerful analytic approach (from among all options considered that yield unbiased intervention effect estimates and correct type 1 error rates) using data from before randomization. Options that will be considered include selecting a single follow-up score (e.g., score documented closest to 12 months) and using all scores within the follow-up window and accounting for correlation of repeated measures within an individual. Additional details on the general simulation approach are provided in Supplement 3, part B, with full details and the final analytic approach to be specified in the standalone statistical analysis plan (SAP) for the trial.

8.3.3 OTHER SECONDARY ANALYSES

Analyses of secondary outcome measures will follow the same general analysis approach as the primary outcome, applying a generalized linear model with appropriate outcome distribution and link function, and using a robust (sandwich) variance estimator. Secondary outcomes that are continuous measures (e.g., days of any medication treatment for OUD) will be analyzed using a parallel approach as for the primary and powered secondary outcome analyses. Models will adjust for health system and for the baseline value of outcome measures (if available), using the continuous version of binary measures where available (e.g., for clinically significant improvement in depressive symptoms we plan to adjust for the baseline PHQ score). Other pre-selected covariates to be adjusted for in the models will be identified using a similar approach as for the primary outcome, pre-specified in the standalone SAP. For binary

secondary outcomes (e.g., sustained buprenorphine treatment for OUD, clinically significant improvement in depressive symptoms), we plan to use a modified Poisson regression with robust variance to estimate a relative rate.[46] For the secondary composite measure of any major adverse event (including opioid OD, other drug OD, suicide attempt or other self-harm, hospitalizations, or death) during the follow-up period, we will apply survival analysis methods for time-to-event data (i.e., time to the first major adverse event). Patients are censored at 12 months (end of follow-up) or disenrollment from the health system (for one of the sites with enrollment information available). Kaplan-Meier curves will be generated and Cox proportional hazards models stratified by health system will be used to estimate hazard ratios. In addition, we may also consider covariate-adjusted estimators for time-to-event outcomes that can improve precision and power[45], such as the targeted minimum loss-based estimator of the difference in restricted mean survival times (RMSTs) at 12 months between intervention and control groups.[47] The final analytic approach will be specified in the standalone SAP for the trial.

8.3.3.1 EXPLANATORY MODERATION ANALYSES

The effect of the intervention on each of the main trial outcomes could be modified by the other main outcome. To address this question, we plan to explore whether, for patients with larger reductions in depressive symptoms, there is a stronger effect of the intervention on days of OUD treatment, as compared to patients with smaller reductions in depressive symptoms; and similarly, whether patients with more days of OUD medication treatment show a stronger effect of the intervention on reductions in depressive symptoms over the study follow-up as compared to patients with fewer days of OUD medication treatment.

8.3.4 ESTIMATING REIMBURSABLE COLLABORATIVE CARE COSTS

8.4 WE WILL ESTIMATE THE PROPORTION OF THE TOTAL NURSE TIME BASED ON FTE AND SALARY THAT WOULD BE REIMBURSABLE USING THE CMS COCM CPT CODES IF ALL PATIENTS (BOTH KPWA AND IUH) WERE COVERED BY CMS (ASSUMING IN THE FUTURE MORE INSURERS WILL HAVE SUCH CODES), AND DESCRIBE HOW IF VARIES ACROSS DIFFERENT DEMOGRAPHIC AND CLINICAL SUBGROUPS (E.G. BY AGE, DEPRESSION SEVERITY, OUD STATUS [BUPRENORPHINE TREATED/UNTREATED], AS WELL AS CONSIDERING MEDICAL, MENTAL HEALTH, AND SUD COMORBIDITY). HANDLING OF MISSING DATA

For our main outcome (Aim 1), we are using EHR prescribing data, health system dispensing and claims data, and prescription monitoring program (PMP) data. Health system-centric data may be incomplete if patients receive medications to treat OUD outside of the health system. The PMP should comprehensively capture buprenorphine prescribing but will be missing if patients move out of state and the PMP does not collect data on naltrexone prescribing. Given most patients with OUD are treated with buprenorphine we expect any missing data for naltrexone from PMP data will have minimum

impact. We are making every effort to obtain PMP data for the study sample but that is not assured given neither site has linked health system and PMP data previously.

To address missing PHQ-9 outcome data bias due to measured factors, our initial plan is to conduct a weighted complete case analysis that uses inverse probability weights constructed using baseline information on each participant. However, if we find that post-baseline covariates significantly predict missing outcome information, we will use multiple imputation to address missing data. We will construct between 25 and 50 imputed data sets and use Rubin's rules to accurately construct standard errors. The final approach to handling missing data will be specified in the standalone SAP for the trial.

Patients will be missing outcome data if they receive care outside the health system or if they do not have a PHQ depression severity score documented in the EHR during the 3-13-month follow-up period. Health information exchange data will be obtained from Indiana state for secondary measures of any adverse health outcome(s). These data are expected to have little if any missing data except when patients move out of state. KPWA is both a delivery system and insurer and is known from prior studies to capture most of these data between the automated records and insurance claims except when a patient disenrolls from the health system. Missing data due to disenrollment is expected to be minimal due to the relatively short (13-month) study follow up period.

9 STUDY OVERSIGHT

9.1 KEY ROLES AND STUDY GOVERNANCE

MULTIPLE PI (CONTACT)	SCIENTIFIC PROJECT SCIENTISIT	NIMH DSMB LIAISON
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9.1.1 STUDY LEADERSHIP TEAM

The study leadership team consists of the multiple PIs, NIMH scientific officer, and lead investigators from Indiana University Health for the study.

9.2 DSMB OVERSIGHT

The NIMH Data and Safety Monitoring Board (DSMB) will provide ongoing oversight for the trial. The Board consists of voting members chosen by NIMH for their relevant expertise. The DMSB operates under the rules of a NIMH-approved charter.

The DSMB will advise NIMH of its findings and reports will be shared with IRBs by the study team, as required. Confidentiality will be maintained during all phases of the DSMB review and deliberations. We will be responsive to additional specific requests for data reports that may be requested by the DSMB.

The NIMH DSMB communicated in December 2019 that oversight of the pilot study was not required.

9.2.1 SCHEDULE AND CONTENT OF DATA AND SAFETY MONITORING REPORTS

The schedule for delivery of the DSMB reports will be determined by the DSMB; three reports per year are expected. DSMB reports will be submitted via email to the Project Officer and DSMB liaison.

Elements that the DSMB needs for the interim and final reports will be clearly defined in advance on a template developed in collaboration with the DSMB liaison and approved by the DSMB. The report will summarize overall trial progress, protocol implementation (violations and deviations), as well as safety and harm reports for each site.

9.2.2 DSMB REVIEW OF PROTOCOL MODIFICATIONS

The DSMB will review and approve major changes to the protocol before changes are implemented at either site; the Board will receive minor changes to the protocol as notifications in the tri-annual data report.

9.3 CRITERIA FOR STOPPING THE STUDY

If, in the opinion of the multiple PIs, NIMH, DSMB or IRB, there is sufficient reasonable cause, written notification documenting the reason for study termination will be provided to the PI and/or NIMH by the terminating party.

Circumstances that may warrant termination include, but are not limited to, the following.

- ***Inadequate enrollment***. Inability to enroll an adequate number of eligible subjects to meet the minimal sample size (n= 800) could result in study termination.
- ***Low intervention engagement and consent rates*.** Low consent and engagement rates—alone—are not a reason for termination of the study. This study is evaluating the proportion of patients who are interested in engaging with the intervention (Aim 3a: “reach”), and the pilot has shown that engagement can take months for this population (Supplement 2). Further, the study is

using formative evaluation to continually improve engagement. In addition, a prior CC trial for alcohol use disorders, several eligible patients reported stopping alcohol use because of the outreach letter and/or recruitment call alone. Nonetheless, if DSMB reports indicated that consent or engagement rates were so low that demonstration of significant effectiveness or benefit was not plausible, then the NIMH, DSMB, or IRB may choose to suspend the study.

- ***Inadequate protection of patient safety.*** If reports indicated the study staff were not following study safety protocols (e.g., for intervention patients who are suicidal), the DSMB could terminate the study.
- ***Evidence of unexpected harm***. Emergence of unexpected, significant, or unacceptable risk to subjects would be reason for termination.

If the project is prematurely terminated or suspended, NIMH will promptly inform the investigators/institutions and the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB will also be informed promptly and provided the reason(s) for the termination or suspension by NIMH or by the investigator/institution, as specified by the applicable regulatory requirement(s).

10 ASSESSMENT OF SAFETY

10.1 INTERVENTION SAFE PRACTICE PROTOCOL, TRACKING AND REPORTING

As above, clinical care for the trial cohort is provided by the health systems and the NCM only has contact with patients randomly sampled for the intervention who consent to participate. For the remainder, and for patient safety issues that arise in the health system, each health system will follow their own safety protocols.

Protocols for safe practices will be followed by NCMs for all consenting MI-CARE intervention participants. A patient may spontaneously report suicidal ideation or another high-risk situation (e.g., overdose, recent relapse) to the NCM or endorse item 9 of the PHQ-9 (about suicidal thoughts) on a study questionnaire. The NCM will assess suicidality for consented patients indicating suicidal thoughts, suicide attempt, or recent overdose (self-reported or documented in the EHR). Whenever suicidal thoughts or other high-risk clinical situations (e.g., overdose, recent suicide attempt) are reported to the NCM (whether incidentally or in a structured assessment) the NCM will prioritize safe practice needs by using the safe practice protocol to:

- Assess the patient's immediate safety;
- Appropriately triage the patient to connect them with appropriate services; and
- Notify the primary care team.

Safe practice protocol use, actions taken, and resolution for each event will be tracked by NCMs for consented MI-CARE participants and summarized in each DSMB report. For review, the safe practice protocol is provided as an attachment to the study protocol.

If a patient spontaneously reports recent suicidality, overdose, or the need for potentially life-saving OUD treatment to an NCM prior to consent, the study nurse will follow the safe practice protocol to ensure that the patient is connected with their primary care team or other appropriate services in the health system.

10.2 MANDATORY REPORTING

Nurses are mandatory reporters. Standard procedures for reporting to the state's Child or Adult Protective Services (CPS, APS) will be followed should a subject voluntarily disclose neglect or abuse. CPS and APS reporting will not be tracked or reported for any study purpose.

10.3 ADVERSE EVENTS (AE) / SERIOUS ADVERSE EVENTS (SAE) AND REPORTING

We aim for harm reports to rely on data sources collected uniformly across study arms and not to include AEs and SAEs observed differentially among patients in the intervention arm. Many events, such as suicide, overdose, hospitalization and/or death may be documented in patients' electronic medical records (EMR) by NCMs (e.g., learned due to NCM outreach after missed appointments). Due to the pragmatic study design, such SAEs will not be observed in the control arm and use of EMR data may introduce bias. We therefore restrict harm monitoring to adverse events that lead to acute care in emergency departments or hospitalization, documentation of which are less likely to be biased by the intervention.

We will report self-harm (e.g., suicide attempt) and opioid or other drug overdose(s), that result in ED visits or hospitalizations (psychiatric and non-psychiatric), and all-cause mortality (by manner of death), in the intervention arm compared to usual care arms. We will include any intentional poisoning (overdose) as a suicide attempt as well. We will report the number, percent, and rate of these serious adverse events (SAEs) in each harm report for the DSMB to review. Formal sequential tests to compare SAEs between arms will not be conducted because the number and rate of events are expected to be too small to be able to detect statistically significant differences. Blinding will be in place to assure that the study team is not looking at outcome data across treatment arms during the trial.

There is a lag between when an event may occur and when the event information is recorded and available in the data sources utilized. To allow sufficient time for data capture, datasets used to generate the DSMB harm reports will be administratively censored according to a plan documented in an approved DSMB report template (up to a 3-month lag). We will be evaluating trial outcomes using a 6-month lag to allow us to maximal time to obtain completed claims and state death records (the latter of which have variable and unpredictable lags up to 24 months in Washington).

10.3.1 REPORTING OF INTERVENTION GROUP DEATHS AND UNEXPECTED AND RELATED SAEs LEARNED OF INCIDENTALLY BY NCM

Any unrelated deaths, and unexpected and related SAEs, that NCMs learn of will be summarized for the DSMB with each report and reported to the NIMH DSMB liaison and program official no later than 5 business days after a principal investigator learns of the death (per NIMH reporting policy). Unexpected and related SAEs will be reported within 10 business days to the same NIMH staff. The patient's care team will also be notified via the EHR.

10.3.2 REPORTING INTERVENTION GROUP HIGH RISK CLINICAL SITUATIONS

The DSMB will review study staff responses to any high-risk clinical situations (e.g., suicidal ideation or behavior) to assure that study staff always prioritize participant safety and follow the safe practice protocol. This information will be provided to the DSMB in the tri-annual reports. Such study staff responses can only be submitted for MI-CARE intervention participants with whom the study has had some contact.

10.4 REPORTING BREACHES OF CONFIDENTIALITY

Breaches of confidentiality will be reported to the DSMB as protocol deviations, not adverse events.

10.5 UNANTICIPATED PROBLEMS AND REPORTING

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets all 3 of the following criteria:

1. Unexpected in terms of nature, severity, or frequency given a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Incidents or events that meet the OHRP criteria for unanticipated problems will be reported to the IRB and the NIMH DSMB. Reporting of Unanticipated Problems to the NIMH Program Official and the NIMH DSMB will be accomplished by submission of an Unanticipated Problem Report via fax or email to the NIMH.

Per HHS regulations 46.103(b)(5), the "appropriate timeframe for satisfying the requirement for prompt reporting will vary depending on the specific nature of the unanticipated problem, the nature of the research associated with the problem, and the entity to which reports are to be submitted." We will follow the NIMH Reportable Events Policy timelines: *https://www.nimh.nih.gov/funding/clinical-research/nimh-reportable-events-policy.shtml.*

- Unanticipated problems involving risks to subjects or others will be reported to the NIMH Program Official and the DSMB liaison within 10 business days of the investigators learning of the event.
- Upon receipt, NIMH staff will review and evaluate the report, investigators' description of the event, and any supporting documentation, and will consult with the NIMH Office of Clinical Research (OCR) as necessary.

11 QUALITY MANAGEMENT AND QUALITY ASSURANCE

11.1 STUDY PROCEDURES

Study operating procedures for this trial are detailed in a Manual of Procedures (MOP). Portions of the MOP may be customized to each health system's unique clinical organization and research infrastructure. Study staff will be trained on the study protocol and MOP prior to fielding; staff training logs will be maintained at each study site in accordance with Good Clinical Practice for the trial. The DSMB Liaison will review the MOP prior to the trial fielding.

11.2 PROTOCOL VIOLATIONS AND DEVIATIONS

11.2.1 DEFINITIONS OF PROTOCOL DIVERGENCES

A ***protocol deviation*** occurs when, without significant consequences, the activities of a study diverge from the IRB-approved protocol. Examples of protocol deviations in this study may include a programming error which results in some eligible patients not being identified and therefore not being outreached, with inconsequential impacts on protocol adherence.

A ***protocol violation*** materially a) reduces the quality or completeness of the data, (b) makes the informed consent process inaccurate, or c) impacts the subject's safety, rights, or welfare. Examples of protocol violations in this trial may include unreported serious adverse events, materially inadequate record keeping, and intentional deviation from protocol, Good Clinical Practice or regulations by study personnel.

11.2.2 DOCUMENTATION AND REPORTING OF PROTOCOL DIVERGENCES

Study staff will report protocol divergences to the site project manager; the site project manager will log all protocol divergences (including the date, study ID(s) affected, root cause, resolution, and reporting

requirements) and share such logs with the local PIs. Each logged event will be flagged as a deviation or violation based on final assessment by the KPWA multiple PIs.

Protocol divergences will be reported to the DSMB as annually in data reports, and to the sIRB per the IRB's reporting requirements. If a protocol violation is an Unanticipated Problem, involves risks to patient safety, or significantly impacts study data integrity, it will be reported to the Program Official and DSMB Liaison within 10 business days of either multiple PI learning of the event.

11.2.3 EVENTS NOT CONSIDERED PROTOCOL DIVERGENCES

The study is designed to mimic clinical care which is flexible and adapts to meet patient needs. A strictly protocolized call regime is not appropriate given the nature of the study. Further, in an encouragement trial, patients decide their level of participation and engagement with different elements of recommended care.

Events not considered divergences from the protocol of the study will not be reported. Examples of such events include but are not limited to:

- The Zelen design relies on enrollment of patients using only automated health system data (i.e., data not methodically collected for research purposes). This may occasionally result in the study enrolling a patient whose enrollment data, after randomization and chart review by a study nurse, may be questionable. Such patients remain in the study and are expected to be randomly distributed between arms. Efforts will be made to refine the automated screening program over time. However, patients enrolled due to a programming error will be reported as protocol violations.
- The information sheet is sent in advance of the oral consent call, at a patient's request.
- Disruption of intervention service delivery (e.g., consented patient drops out/back in, patient declines and later opts in, patient moves out of State). Note that NCMs may only provide care within state(s) in which they are clinically licensed.
- Patient non-adherence to the planned schedule of study contacts or appointments, such as:
    - More frequent CC calls due to changes in clinical scenario (e.g., patient becomes acutely unstable, relapses to opioid use, has worsening mental health symptoms);
    - Pausing of recruitment outreach or CC by the NCM for clinical reasons (e.g., acute health event, hospitalization, post-discharge coordination period);
    - Pausing of recruitment outreach or CC due to other extenuating circumstances, (e.g., away at inpatient treatment, incarcerated; traveling out of state temporarily);
    - Patient is difficult to reach or maintain contact with (e.g., housing instability, intermittent access to phone or internet);
    - Participant preference is for less frequent NCM CC appointments.

- A patient loses their PCP or leaves the health system; the study will continue to reach out to offer the program, work with others on the patient's care team, and support the patient in establishing care with a new PCP.
- Patient or PCP non-adherence to expert consultants' recommendations (e.g., patient chooses not to start medications recommended to treat OUD, primary care team does not implement recommendation);
- The NCM administers assessments by phone rather than via REDCap and/or assessments are abbreviated due to patient preference or abilities (e.g., patient cognitively over-burdened by full set of questions)
- An NCM opportunistically has an in-person visit with a MI-CARE participant at a health system clinic convenient to both parties; alternatively, an NCM meets in-clinic with members of a patient's care team.
- Care transition with the patient takes place +/- 4 weeks from the patient's 12-month window end date due to difficulty re-contacting the patient.

11.3 QUALITY MANAGMENT

A Quality Management Plan (QMP) has been created to establish guidelines for tasks related to the trial. The QMP includes a detailed description of quality management activities applicable to the study, including:

- Essential documents;
- Study staff training and qualifications logs;
- Review of study records for completeness and accuracy;
- Logs of issues encountered (e.g., technical problems, protocol divergences, memos to file, etc.).

The QMP describes how and how often internal quality management assessments will be conducted by the research team at each health system, and how and when findings will be summarized and reported to NIMH staff. The QMP is complemented by several quality management tools used in the review process. The DSMB Liaison will review the QMP prior to the trial fielding.

The QMP is a living document that is updated throughout the life of the project, as necessary. The plan will be reviewed at least annually, and any necessary updates made. Edits to the QMP will be reviewed by the DSMB Liaison.

12 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 CONFIDENTIALITY

12.1.1 CERTIFICATE OF CONFIDENTIALITY

Certificate of Confidentiality are intended to protect data collected specifically for research that could be subpoenaed and place a patient at risk. The National Institutes of Health have granted a Certificate of Confidentiality for this study, adding an extra layer of protection to research data (e.g., REDCap databases, audio-recordings, analytic files, PMP data) created to carry out the study.

Certificates of Confidentiality are not applicable to EHR data or anything the NCM adds to the medical record. These records can be subpoenaed separately (i.e., are not protected by a Certificate of Confidentiality). Medical records are protected under HIPAA.

12.1.2 ADDITIONAL PROTECTIONS OF SUBJECT CONFIDENTIALITY

Data and all identifying information will be held in strict confidence. Appropriate steps will be taken to safeguard patient confidentiality, including the following:

- Institutional-, individual-, and software-level access granted by the local information security office and simultaneous knowledge of both a valid username and password are required to access data collected in electronic records;
- Data, including audio-files, are transferred using a secure file transfer platform (after all necessary approvals and agreements are in place);
- All electronic data are maintained on secure health system servers and only project staff are granted access;
- Analytic data files created for research use will include no identifying information (e.g., name, medical record number, birth date) and all data records used for research analyses will be identified only by a unique study identifier;
- The variables calculated for research analyses are not specific enough to allow “backward identification” of individual patients;
- Audio-recordings for clinical supervision will be saved in secure locations with limited access rights to those who require it to perform their specific study duties. No audio recordings of calls with participants will be transcribed.
- Access to computerized medical records (EHR) is controlled by “strong” password protection and automatic “time-outs” for terminals left unattended. All system access is logged, and all usage monitored for evidence of inappropriate access. Inappropriate access or disclosure are grounds for disciplinary action including termination of employment.

Authorized representatives of the NIMH may inspect records, as needed.

12.1.3 SPECIAL PRIVACY CONSIDERATIONS: 42 CFR PART II

The Federal regulation 42 CFR Part II is designed to protect the confidentiality of people who seek substance use disorders treatment. Specifically, 42 CFR Part II protects *"patient records created by federally assisted programs for the treatment of substance use disorders (SUD).* Part 2 has been revised (2017) and refined (July 2020) *"to further facilitate better coordination of care in response to the opioid epidemic while maintaining its confidentiality protections against unauthorized disclosure and use."*[54] While 42 CFR Part II covered data can be used by a legal business owner and disclosed for research under a waiver under HIPAA and Common Rule (e.g. for linkage to PMP data), redisclosure in which a patient can be identified is not allowed.

To avoid a chance of redisclosure, we exclude all diagnoses known to originate from 42 CFR Part 2 covered programs from our computerized algorithm for identifying potentially eligible patients for the trial. This includes largely programs outside KPWA and IUH, but also some internal 42 CFR covered (specialty addiction) programs. If patients have not granted release of data from internal KPWA or IUH 42 CFR Part II programs (allowing their health information to be used for other internal health care purposes), such internal data are excluded from the automated identification of eligible patients and is not visible to NCMs in the medical record, by default in the EHR.

Linkage of the trial sample to State PMPs would be covered under state IRBs and respective DUAs. Data received back from the PMPs will be reduced to a limited dataset before sending to another site (e.g. to combine data from both IUH and KPWA in Indiana). This is permitted under 42 CFR Part II because we will not disclose covered data to PMP, and PMP data (i.e. pharmacy data) are not covered by 42 CFR Part II either, so we will be able to disclose a limited dataset (i.e. this will be the first disclosure, and not a re-disclosure under 42 CFR Part II.

For patients randomized to the CC arm of the trial, health information obtained by NCMs from 42 CFR Part II covered entities will not be placed in patients' EHRs by NCMs without patients' written permission. If a consenting MI-CARE intervention participant receives care from a 42 CFR Part II covered program and 42 CFR Part II covered data is to be collected from the program and placed in the EHR, NCMs will obtain a written release of information for the patient's EHR record (using the standard health care system process) for documentation.

12.2 INSTITUTIONAL REVIEW BOARD

The protocol and study materials have been submitted to a single, centralized IRB (Advarra) for review. IRB approval and waivers of consent and HIPAA authorization applicable to the pilot study and the Zelen design were obtained in September 2020 for the protocol and trial.

Protocol modifications made for the full trial will be approved by the IRB before any human subjects activities are initiated for the trial. Amendments require IRB review and approval before changes are implemented at either site.

12.3 INFORMED CONSENT PROCESS

See Section 6.3 for a description of the modified, verbal consent process for intervention arm patients. NCMs will only outreach to the 50% of subjects randomly selected for the offer of the CC intervention, and the consent process will focus only on the offer of CC.

The study information sheet has been written with the aim of using plain language, minimizing the cognitive burden, and separating clearly what are study activities vs. clinical care (e.g., risks section).

12.3.1 PARTIAL DISCLOSURE OF STUDY RELATED ACTIVIES

During recruitment and consent for the MI-CARE program, patients randomized to be offered the intervention are told that the program is for patients with stress or low mood, who take or used to take opioids.

The oral consent process does not fully disclose all study-related activities.

During recruitment of patients randomized to be offered the intervention, the NCMs do not disclose that:

(1) People are only eligible for the trial if they have an indication that they have OUD in their EHR in the past year;
(2) Their health data will be included in study outcome analyses, or that they may not opt out of this data being included in trial analyses, (to preserve the integrity of the Zelen design);
(3) That we are testing an intervention designed to engage non-treatment seeing patients with OUD into evidence-based medication treatment for OUD; and
(4) That the outcomes of the trial are only partly focused on depressive symptoms; the primary outcome is days of medication treatment for OUD.

This partial disclosure of study related activities is acceptable because:

1) The trial and trial analyses pose no more than minimal risk to intervention arm participants;
2) Trial analyses rely solely on secondary data sources (other studies using only secondary data for analyses are exempt);
3) The waiver does not adversely affect the rights or welfare of subjects. Patients are informed we are studying the offer of extra support from a NCM, in addition to usual care. They are free to decline participation in CC without impacting their welfare or right to health care services;
4) The important question about whether proactive outreach to patients with OUD and significant mental health symptoms can increase access to evidence-based OUD treatment and potentially improve important clinical care like suicide, overdose and death—could not practicably be carried out without the waiver of documentation and alteration of consent; and
5) As appropriate over time, NCMs will share information about OUD treatment options as well as provide added information about the goals of the study (e.g., increasing access to evidence-based treatment for OUD).

6) In addition, as the trial progresses, the NCM will elicit patient perspectives on how the program might be improved, including sharing further details about the goals of the study in these debriefs.

12.3.2 SPECIAL CONSIDERATION, RESEARCH INVOLVING PRISONERS: 45 CFR 46 SUBPART C

This study does not target prisoners as subjects; however, we expect that patients with OUD and co-occurring mental health conditional will be at increased risk of justice-involvement compared to the general population. As such, it is possible that intervention arm patients could become incarcerated, placed under house arrest, or put on parole as deferred prosecution while in the 12-month CC program. We believe that this study meets the requirements of 45 CFS 46.306 because:

- The CC program has the intent and a reasonable probability of improving the health and/or well-being of participant by supporting treatment for OUD, depression and other common conditions (e.g., other substance use, anxiety, pain).
- Any possible advantages to the patients in the CC program are not so great as to bias or impair the participant's decision making while in a limited choice environment (e.g., standard, evidence-based treatments; subjects are not compensated; CC is not in person but virtual);
- The risks involved in the research are commensurate with risks that would be accepted by non-justice-involved participants (primarily, breach of confidentiality for this minimal-risk study);
- Procedures for the selection of subjects is based on clinical criteria and is in no way related to justice-involvement;
- The study information sheet and consent script used plain language; and,
- Patients who become prisoners while in CC will be clearly informed in advance that participation in the study will have no direct effect on his or her parole.

Taking into account that only a handful of CC patients are expected become justice-involved, we do not expect that the IRB would find a need for follow-up examination or care of participants after the end of their participation. The intervention continues to be provided within the IUH and KPWA health systems. Participants are informed of this during the consent process. We believe that the standards of care, clinical documentation (e.g., EHR) requirements, and clinical supervision by health system managers, clinical experts and study team members provide adequate provision for such examination or care.

13 DATA HANDLING AND RECORD KEEPING

13.1 QUALITY AND ACQUISITION OF AUTOMATED DATA FOR ANALYSES

All data needed to implement the SAP for the trial will be collected from automated data sources both internal (e.g., EHRs) and external to the health systems (e.g., insurance claims or HIE, PMP). The study will conduct routine checks of data collected from electronic health systems and look for data anomalies (e.g., missing, out of range). These data sources will be:

	KPWA	IUH	SOURCE
Electronic health system records	☒	☒	EHR, data warehouses
External hospital and emergency dept use	☐	☒	Indiana health information exchange
External hospital and emergency dept use	☒	☐	Insurance claims
Buprenorphine and other opioid data	☒	☒	State Prescription Monitoring Programs, claims, EHR records
Buprenorphine and other opioid data	☒	☐	Pharmacy data, Insurance claims
Buprenorphine and other opioid data	☐	☒	Indiana health information exchange
Death records	☒	☒	State departments of health

Research staff at KPWA and IUH may need to conduct targeted manual chart reviews to understand data for specific patients with data anomalies (e.g., duplicate orders, two hospital stays on the same day, hospital discharge date precedes the admit date). In addition, focused structured chart abstraction will be conducted for all study enrollees to validate quality (and potentially supplement) automated EHR data regarding patient clinical and demographic characteristics and receipt of study-relevant clinical services at the time of study enrollment. Such information may serve as important predictors of study outcomes. While conducting these chart reviews, our abstractors will also review the electronic health record for any known patient death data (e.g., date of death, cause of death, etc.). Although we hope to receive the most complete validated death data from Washington state via our pre-existing KPWA institutional data sharing agreement, we may not be given approval to send the state data to the Indiana honest broker site where we'll be conducting our trial analyses. We will transfer the most complete death data we are able to gather from the EHR chart abstractions, pending availability of the state death data and approval to transfer it to Indiana.

13.1.1 RETROSPECTIVE COHORT ANALYSIS

Before and during the trial, a secondary dataset—with data from before the start of the trial—is used to conduct quality checks on programming code and perform necessary simulations. This will be a retrospective cohort of KPWA and IUH patients meeting trial inclusion criteria over a 25-month period prior to randomization, with data collected during a 4-year period including 2 years prior to the sample eligibility period. Specifically, this retrospective cohort analysis will be used for two key data and analytic quality purposes:

- To allow quality assurance on our computer code for final trial sample specifications, and final outcome measures and covariates for the main trial, including data coding, cleaning and quality checks. Based on preliminary analyses, the ongoing pilot study, and new results in the publish literature, refinements have been made to inclusion and exclusion criteria, and measure specifications, which necessitate this important quality assurance work.
- To perform modeling that will inform final statistical approaches. This includes simulations on a sample that had an index PHQ-9 of 10 or more between over a 1-year period and allows covariate data from 2-years prior to index PHQ-9 score, and follow-up data over the 13 months after the index PHQ score. Simulations will address covariates to adjust for in primary analyses to improve power (Aim 1). These are described fully in Supplement 3. Additional simulations address which follow up PHQ-2 or PHQ-9 score to use if patients have multiple, only PHQ-2, or no follow-up scores in the 12-month window (Aim 2).
- Refining/debugging of code for main analyses before trial outcomes data are available.

These activities are intended to allow coding and rapid analysis of final trial data during the 2 months after complete trial data become available (April-May 2024).

An additional waiver of consent and HIPAA is sought from the IRB to collect and utilize these data for the purposes stated above.

13.2 QUALITY AND ACQUISITION OF OTHER STUDY DATA

The study will use 21 CFR Part 11-compliant data capture systems (e.g., REDCap) to document:

- Oral consent;
- The monitoring of symptoms of depression, OUD and other common conditions for measurement-based care;
- Interventional components used (e.g., conditions addressed, current external treatments, BA conditions targeted that session);
- Metrics for formative evaluation;
- Metrics for economic analyses; and
- Information for general case management by the NCM (e.g., data systems will include password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

Data will be captured directly in the system (not entered from hardcopy originals). Quality checks will be periodically conducted to identify any data anomalies.

13.3 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of study staff at each enrollment site and under the supervision of the site investigators. The site principal investigators will be responsible for ensuring the accuracy, completeness, and timeliness of the data reported.

Each enrollment site is responsible for obtaining and quality checking data received from State sources (e.g., PMP, death and HIE records). Study programmers will extract, quality check and transform health system records to the study's data dictionary specifications using coded SAS® programs.

To obtain state PMP data, after each site obtains state IRB approval, bidirectional data use agreements will be arranged to allow linkage and transfer of data sets, or analysis on an honest broker site approved by the state. IUH will securely transfer limited data sets (not including Indiana PMP data) to KPWA, which serves as the data coordinating center, under the terms of a data use agreement. KPWA will then create and securely transfer a limited data set with both KPWA (including Washington PMP data) and IUH data needed for the final trial analysis to the IUH honest broker site to merge with the IUH PMP data (which cannot leave the state of Indiana).Only specific data team members (i.e. biostatisticians, data scientists, programmers) will have access to the full trial dataset on the Indiana honest broker site, per the terms of a separate data use agreement per personnel accessing the enhanced research environment.

Analytic data sets will be created without any values being overwritten by project staff. Values may be recoded into new variables for analyses, to preserve the original record. Final analytic datasets will be saved electronically, clearly labeled and stored in a secure project folder on the KPWHRI server accessible only to project staff.

13.4 STUDY RECORDS RETENTION

Identifying information, linking files and original audio recordings will be destroyed within 7 years of the conclusion of the project award unless consent to retain these files is granted by the IRB. All components are minimal risk. Consent-related documents and other study materials are maintained separately from the protocol and protocol appendices.

13.5 DATA SHARING POLICY

The study team is committed to sharing data created by the trial, limited only by the need to protect the privacy of potentially identifiable health information in accordance with HEAL policies, State PMP policies, and proprietary data about the participating health care systems. Any datasets for public distribution will be fully de-identified in compliance with HIPAA standard for de-identification and will not identify sites.

13.6 PUBLICATION POLICY

Each publication, press release, or other document about this NIH-funded research study must include an acknowledgment and disclaimer such as:

"Research reported in this publication was supported by the National Institute of Mental Health of the National Institutes of Health under Award Number UF1MH121949. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health."

The NIMH will be notified in advance of any press release concerning the outcome of this research, for coordination purposes.

14 ABBREVIATIONS

AE / SAE	Adverse Event / Serious Adverse Event
ANCOVA	Analysis of Covariance
BA	Behavioral Activation
CBT	Cognitive Behavioral Therapy
CC	Collaborative Care
CFR	Code of Federal Regulations
CPT	Current Procedural Terminology
DSMB	Data and Safety Monitoring Board
ED	Emergency Department
EHR	Electronic Health Record
FDA	Food and Drug Administration
HEAL	Helping to End Addiction Long-term
HIE	Health Information Exchange
HIPAA	Health Information Portability and Accountability Act
ICD	International Classification of Disease
IRB	Institutional Review Board
ITT	Intent to Treat
IU / IUH	Indiana University / Indiana University Health
KPWA	Kaiser Permanente Washington
KPWHRI	Kaiser Permanente Washington Health Research Institute
MBC	Measurement-based care
MCID	Minimal Clinically Important Difference
MDD	Minimal Detective Difference
MI	Motivational Interviewing
MI-CARE	More Individualized Care: Assessment and Recovery through Engagement
MME	Morphine Milligram Equivalents
MOP	Manual of Procedures
NCM	Nurse Care Manager
NIH	National Institutes of Health
NIMH	National Institute of Mental Health, NIH

OCR	Office of Clinical Research
OD	Overdose
OHRP	Office of Human Research Protections
OUD	Opioid Use Disorder
PC / PCP	Primary Care / Primary Care Provider
PHQ	Patient Health Questionnaire
PI	Principal Investigator
PMP	Prescription Monitoring Program
PTSD	Post-Traumatic Stress Disorder
QMP	Quality Management Plan
QQ	Quantile-Quantile
REDCap	Research Electronic Data Capture
RMST	Restricted Mean Survival Times
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis Software®
SD	Standard Deviation
SE	Standard Error

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APPENDICES - PROTOCOLS FOR OTHER RESEARCH ACTIVITIES

Additional study activities can be found in the following protocols. These activities support(ed) the development and evaluation of the MI-CARE intervention to be tested in the pragmatic trial. While these activities were approved by the IRB, DSMB oversight was not required.

- MI-CARE Pilot Study protocol
- Appendix A: Pre-Trial Secondary data analyses protocol
- Appendix B: Pre-Trial Phone interview study protocol (KPWA only)
- Appendix C: Pre-Trial Clinical Workflow design meetings protocol

OTHER STUDY MATERIALS FOR TRIAL

All components are minimal risk. Consent-related documents and other study materials submitted to the IRB for approval are maintained separately from the protocol and protocol appendices. These materials are not considered part of the protocol itself.

SUPPLEMENTS TO THE TRIAL PROTOCOL

Additional information relating to the trial protocol are provided in 4 supplements:

- ***Supplement 1***: Rationale and justification for waivers of consent and HIPAA authorization required to obtain valid study outcomes for the encouragement trial (Zelen design).
- ***Supplement 2***: Detailed justification and rationale, based on pre-trial activities, for refinements to the main pragmatic trial sample specifications, recruitment and consent processes, measures specifications, and statistical analysis and power – as reflected in this protocol document.
- ***Supplement 3***: Detail on simulation approaches to inform power analyses for primary outcome and secondary study outcome data points.
- ***Supplement 4***: Detailed justification and rationale on the formative evaluation qualitative interviews to be conducted with staff delivering the MI-CARE intervention and the OBAT nurses supporting treatment.