Collaborating to Heal Addiction and Mental Health in Primary care (CHAMP)

Protocol Number: MH121942

National Clinical Trial (NCT) Identified Number: NCT04600414

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Sponsor: National Institute of Mental Health (NIMH)

Grant Title: Collaborating to Heal Addiction and Mental Health in Primary care (CHAMP)

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Summary of Notifications/Clarifications made from Previous Version:

We have attached a revised DSMB Protocol for the board's review.

Affected Section(s)	Summary of Revisions for the March 202 DSMB meeting	Rationale
3.0 Objectives and Endpoints	Tertiary/Exploratory Objective and Hypothesis – Revised from comparing clinics randomized to low and high intensity sustainability strategies to conducting a pre-post evaluation.	Because we extended the recruitment period for the effectiveness trial, there was insufficient time to conduct the implementation trial.
4.1 Overall Design	Overall Design – Sustainability Implementation trial changed to Pre-Post Sustainability Evaluation Specific Aims and Hypotheses – Revised Specific Aim #3 from comparing clinics randomized to low and high intensity sustainability strategies to conducting a pre-post sustainability evaluation. Randomization – Dropped randomization for Specific Aim #3.	Because we extended the recruitment period for the effectiveness trial, there was insufficient time to conduct the implementation trial. Because we are now planning to conduct a pre-post analysis, there is no need for randomization.
9.1 Statistical Hypotheses	Exploratory Hypothesis for Exploratory Aim – Revised exploratory hypothesis from comparing clinics randomized to low and high intensity sustainability strategies to conducting a pre-post sustainability evaluation.	Because we extended the recruitment period for the effectiveness trial, there was insufficient time to conduct the implementation trial.
9.2 Sample Size Determination	Dropped sample size determination for Specific Aim #3	Because we are not conducting the implementation trial, there is no need for a sample size determination.
9.4.6 Exploratory Analyses	Exploratory Outcomes – Changed number of participating clinics and the timeframe for the pre-post sustainability evaluation. Quantitative Analysis - Changed number of participating clinics and the timeframe for the pre-post sustainability evaluation. Qualitative Analysis – Added a qualitative data collection and analysis component to the exploratory analyses.	Because not all clinics wanted to participate in the sustainability evaluation, there were fewer clinics than anticipated. Because we extended the recruitment period for the effectiveness trial, there was less time for the pre-post sustainability evaluation. Because of the small sample of clinics, we added a qualitative component to the exploratory analyses to yield richer findings.

CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the NIH terms of award.

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STATEMENT OF COMPLIANCE

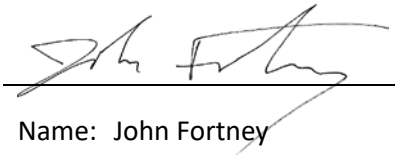
The trial will be conducted in accordance with International Council on Harmonization Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the NIMH Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials willbe submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained from both the IRB and NIMH DSMB before any participant is consented. Any amendment to the protocol will require review and approval by the IRB and the DSMB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator or Clinical Site Investigator:

Signed:  Date: 02/16/2024

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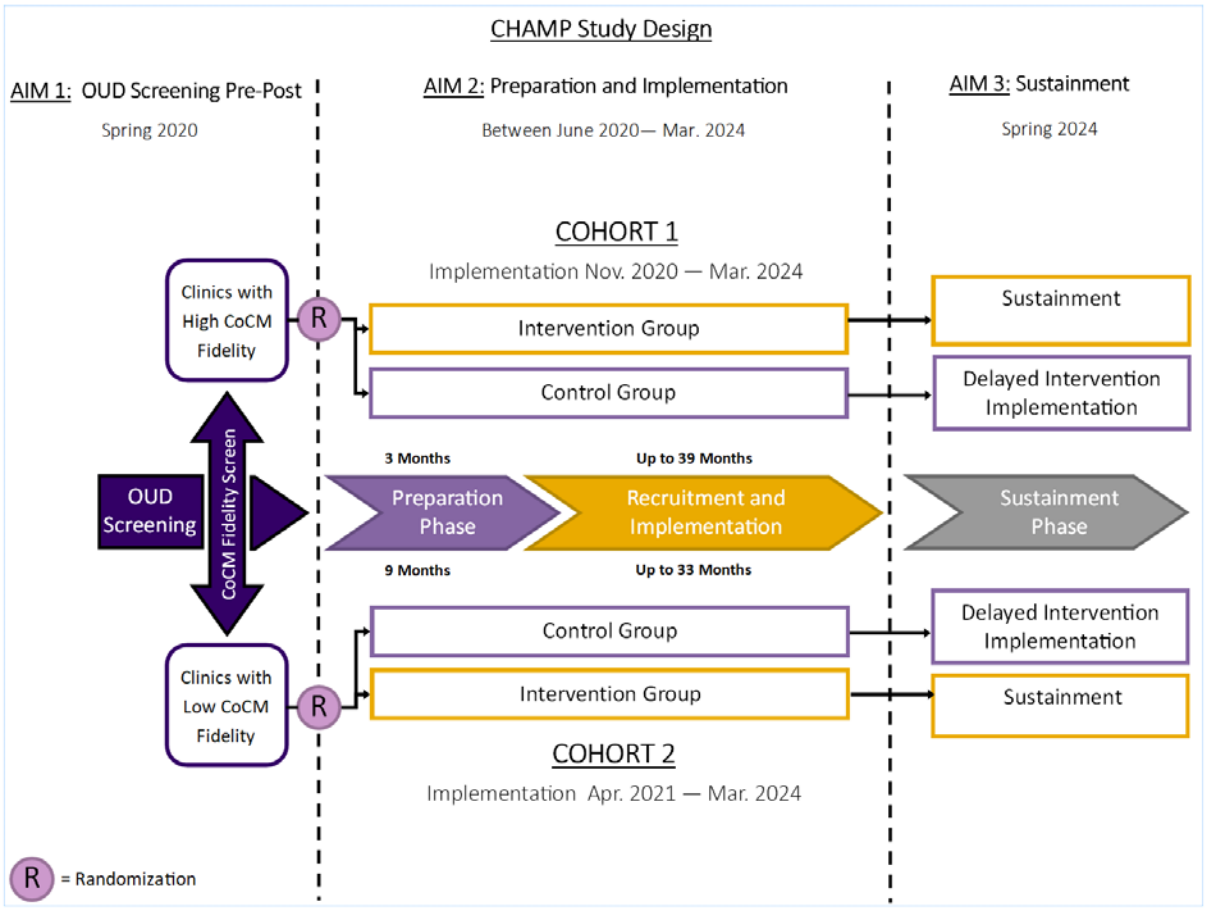
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title	Collaborating to Heal Addiction and Mental Health in Primary care (CHAMP)
Grant Number	MH121942
Study Description	The gold-standard intervention for Opioid Use Disorder (OUD) is Medication for Opioid Use Disorder (MOUD). Because more patients with OUD need access to MOUD in primary care, we are testing whether the Collaborative Care model (CoCM) is effective at treating both mental health symptoms (MHS) and OUD concurrently in primary care settings. The intervention is CoCM for MHSand OUD. The active control is CoCM for MHS, but not treating OUD. The *primary objective* is to compare patient-reported outcomes in the intervention and control groups, and will be tested with in an Effectiveness trial. The *secondary objective* is to compare the detection of OUD pre- versus post-OUD screening implementation, and will be tested using a Pre-Post trial design. The exploratory objective is to compare intervention clinics randomized to a low-intensity sustainability implementation strategy or a high-intensity sustainability strategy, and will be tested in an Implementation trial.
Objectives	The CHAMP study addresses three important objectives including: **Primary Objective** - Does implementing Collaborative Care for OUD and MHS improve MHS and OUD outcomes? **Secondary Objective** - Can OUD screening be effectively incorporated into primary care mental health screening protocols? **Exploratory Objective** - What implementation strategies are effective at sustaining Collaborative Care programs that concurrently manage mental health disorders and OUD?
Endpoints	The *multiple* primary outcomes for the Effectiveness trial are self-reported use of opioids and mental health functioning.
Study Population	We will recruit 1,200 adult primary care patients screening positive for OUD and MHS from 42 clinics in 11 states and the District of Columbia. Age, gender and race/ethnicity will be representative of the demographics and epidemiology of the clinics.
Description of Sites/Facilities Enrolling Participants	Sites include a range of primary care settings in the United States. Fourty-two clinics from 15 healthcare systems.
Description of Study Intervention/Experimental Manipulation	Collaborative Care - The treatment of OUD will be integrated with the treatment of MHDs, other substance use disorders (SUDs), and physical health disorders in the primary care setting. Primary care providers will prescribe MOUD in consultation with a psychiatrist and support from a care manager who will also provide brief psychotherapy.
Study Duration	The Effectiveness trial will be 39 months in duration.
Participant Duration	Those enrolled in the Effectiveness trial will participate for 6 months.

1.2 SCHEMA


CHAMP Study Design
AIM 1: OUD Screening Pre-Post
Spring 2020
AIM 2: Preparation and Implementation
Between June 2020— Mar. 2024
AIM 3: Sustainment
Spring 2024
COHORT 1
Implementation Nov. 2020 — Mar. 2024
Clinics with High CoCM Fidelity
R
Intervention Group
Control Group
Sustainment
Delayed Intervention Implementation
OUD Screening
CoCM Fidelity Screen
3 Months
Up to 39 Months
Preparation Phase
Recruitment and Implementation
Sustainment Phase
9 Months
Up to 33 Months
Control Group
Intervention Group
Delayed Intervention Implementation
Sustainment
Clinics with Low CoCM Fidelity
R
COHORT 2
Implementation Apr. 2021 — Mar. 2024
R = Randomization

1.3 SCHEDULE OF ACTIVITIES

	Pre-consent	Baseline Day 1-14	Multiple Visits Day 1-90	3 Month Follow-Up	Multiple Visits Day 91-181	6 Month Follow-Up
Clinic Randomization	X					
Screen for OUD -NIDA–Assist (OUD Items) -Short Opioid Screen (SOS)	X					
Eligibility Assessment - PHQ-9 - GAD-7 - PC-PTSD-5 - OUD DSM5 Checklist OR OUD diagnosis documented in the electronic health record.	X					
Informed Consent	X					
Encounter with Primary Care Provider			X		X	
Encounter with Care Manager - PHQ-9 - GAD-7 - PCL-5 - Opioid use, withdrawal, craving, side-effects			X		X	
Psychiatric Case Review			X		X	
Outcome Evaluation						
Demographics		X				
Drug Use - BAM-R		X		X		X
Mental Health Symptoms - SCL20 - Neuro-QOL Anxiety – Short Form - PCL-5 -Audit/Audit-C -Veterans Short Form-12		X		X		X
Attitudes and Beliefs - Readiness to Change-ICR - Assessment of Perceived Access to Care		X X		X		X
Recent Service Use				X		X
Adverse Events Reporting		X	X	X	X	X

2 INTRODUCTION

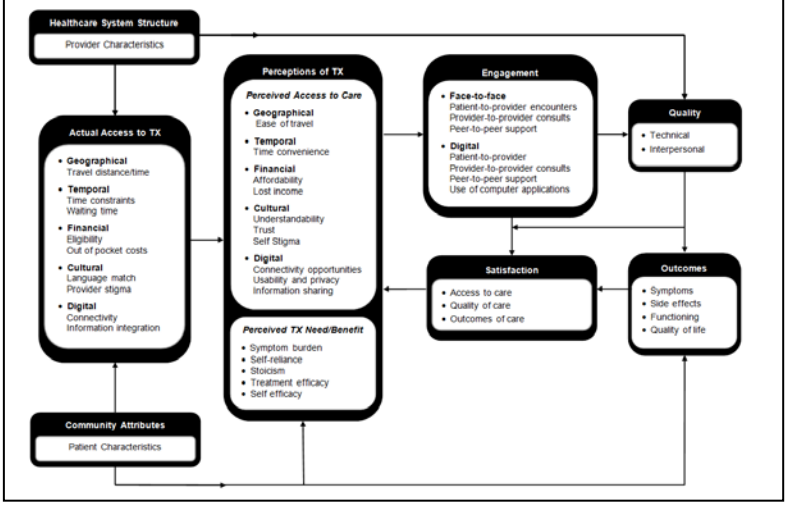
2.1 STUDY RATIONALE

An estimated 11.4 million Americans misuse opioids, and 2.1 million have an Opioid Use Disorder (OUD). Medication for OUD (MOUD) is the gold-standard treatment for OUD, but is not offered in most primary care settings. As a result, only 20% of Americans with OUD receive any addiction treatment. While MOUD could prevent many of the estimated 47,600 fatal opioid overdoses a year (130 per day), we currently lack the means to deliver this treatment to the majority of people who need it. Making MOUD for OUD more widely available in *primary care settings* could help address this national crisis. The Collaborative Care Model (CoCM) is a primary care- based intervention developed at the University of Washington that improves access to effective treatments for a wide range of Mental Health Disorders (MHD). CoCM has the potential to substantially improve access to MOUD for patients with co-occurring OUD and MHS.

2.2 BACKGROUND

Excessive opioid use is a national emergency. There were >350,000 emergency department visits in 2015 due to opioid poisoning.[1] There were 47,600 opioid overdose deaths in 2017,[2] and the death rate is growing fastest in rural areas (325% since 1999).[3] There are an estimated 2.1 million Americans meeting diagnostic criteria for an OUD, including 1.7 million with a prescription pain reliever use disorder and 0.7 million with a heroin use disorder.[4] Medication Assisted Treatment (MAT) with either buprenorphine, methadone, or naltrexone represents the gold-standard intervention for OUD[5] and significantly reduces risk for overdose or death.[6] However, only 20% of Americans with OUD received any formal or informal addiction treatment in the past year.[7] Moreover, even in addiction treatment settings in the US, only 32% of patients with OUD were prescribed MOUD in 2016.[8] Lack of *access* and *engagement* in MOUD is clearly a driver of poor OUD outcomes, especially in rural areas lacking addiction services.

Figure 1 – Theory of Access and Engagement



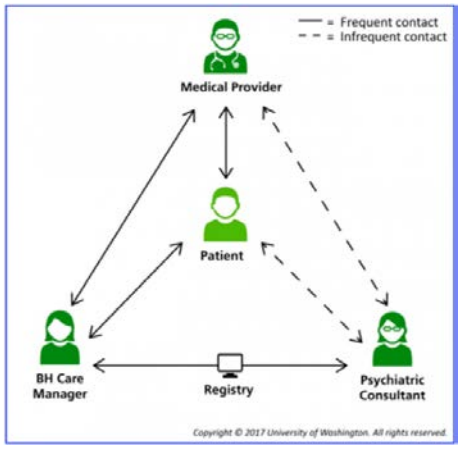
To close this *engagement* gap, more patients with OUD need *access* to MOUD in primary care settings.[9,10] We conceptualize *access* to care as the potential ease of having encounters with a broad array of healthcare providers (Figure 1).[11] Integrating OUD treatment into primary care improves geographical (i.e., travel), temporal (e.g., wait time), and cultural (e.g., stigma) access. Our conceptualization of *engagement* is participating sufficiently in a treatment plan to potentially experience a therapeutic effect. Treatment engagement depends on patient perceptions about access to care, and the perceived need for and expectations from treatment.[11] With adequate access and engagement, individuals have the opportunity to receive high *quality* care and improved

outcomes. However, MOUD delivered in primary care can only improve outcomes if the quality of care is high.

Unfortunately, there are barriers to providing high quality MOUD in primary care, especially in rural areas. Federal regulations prevent prescribing methadone for MOUD in primary care.[12] Naltrexone requires complete withdrawal from opioids for 7-10 days, which is difficult to achieve in an outpatient setting. For buprenorphine, training (8 hours for primary care physicians and 24 hours for mid-level providers) must be completed in order to receive a DATA 2000 waiver to prescribe, and 56% of rural counties do not have any providers with a waiver.[13] In addition, primary care providers report inadequate expertise in addiction treatment, lack of institutional support, insufficient remuneration, and limited ancillary support.[14,15] However, the biggest barrier to MAT, according to both primary care providers who do and do not prescribe buprenorphine, is the lack of support for treating MHDs.[15] Over the last 25 years, models of integrated care have emerged that provide the support needed by primary care providers to effectively manage MHDs, such as depression and anxiety disorders, and we believe that a similar cultural shift is possible for MOUD for OUD.

CoCM is an evidence-based model of integrated care developed by the Department of Psychiatry at the University of Washington.[16,17] CoCM operationalizes the principles of the chronic care model to improve access to evidence-based MHD treatments for primary care patients. CoCM is based on six key principles: 1) evidence-based, 2) measurement-based, 3) team-based (Figure 2), 4) population-based, 5) patient-centered, and 6) accountable.[18] CoCM supports the delivery of evidence-based pharmacological and psychosocial treatments. CoCM is measurement-based with screening and monitoring of patient-reported outcomes over time to assess treatment response and facilitate treatment adjustments.[19] CoCM is team-based led by a primary care provider with support from a care manager in consultation with a psychiatrist who provides treatment recommendations for patients who are not achieving clinical goals. CoCM is population-based whereby a registry[20,21] is used to monitor treatment engagement and facilitate the identification of patients falling through the cracks. CoCM is **patient-centered** with proactive outreach to engage and activate patients, shared decision making, and support for treatment adherence and self-management. Collaborative care is accountable with continuous quality improvement to meet clinic performance benchmarks.

Figure 2. Collaborative Care Model



Evidence for CoCM - Meta-analysis demonstrates that CoCM is cost-effective across diverse practice settings, patient populations, and disorders.[22] Co-I Unützer conducted Project IMPACT, the *definitive* study demonstrating the cost-effectiveness of CoCM for depression (n=1,801).[23,24] Other CoCM trials conducted at the University of Washington demonstrate its effectiveness for anxiety disorders,[25,26] *_ENREF_24* postpartum depression[27] and PTSD.[28] MPI Fortney conducted three trials (∑n=1,024) demonstrating the cost-effectiveness of telepsychiatry CoCM for rural patients.[29-34]

Integrated OUD Treatment - Patients in OUD treatment have high rates of co-occurring MHS.[35-37] Thus, concurrent treatment of OUD and MHS has great potential.[38-40] CoCM represents an ideal approach to co-managing OUD and MHS.[41,42] Yet, little rigorous research has examined the co-management of OUD and MHS, and the evidence to date is mixed. One trial with patients in methadone treatment found that those with MHSs randomized to evidence based psychotherapy had fewer psychiatric symptoms AND

less illicit opioid use.[43] Of the three antidepressant trials with patients in methadone treatment, two demonstrated positive benefits of tricyclics (for depression symptoms but not OUD outcomes)[44,45] and one found no benefit of an SSRI.[46] Importantly, the one previous CoCM trial focused on patients with OUDs and alcohol use disorders (SUMMIT trial) found that the proportion of patients remaining abstinent from opioids in the past 30 days was no higher in the CoCM group than the usual care group (p=.33).[47] However, only 13.4% of the patients in the CoCM group received MOUD compared to 12.6% in usual care (p=.053)[47] suggesting that difficulties with *implementation* were driving results rather than the ineffectiveness of MOUD in the context of CoCM. This highlights the critical importance of using effective implementation strategies to support the delivery of MOUD for OUD in the context of CoCM for MHS.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Psychological distress - Some of the survey questions may make participants feel uncomfortable. An example of such a question is "*Overall, in the past two weeks how much were you distressed by thoughts of ending your life?*"

Loss of Confidentiality - A risk of participating in this study is possible loss of privacy.

2.3.2 KNOWN POTENTIAL BENEFITS

Meta-analysis of collaborative trials has demonstrated significant clinical benefits to participants. While collaborative care will be available to patients at participating clinics who do not enroll in the trial, all patients enrolling in the Effectiveness trial will receive treatment from the collaborative care team. We do not know if patients at clinics randomized to the intervention will benefit more than patients at clinics randomized to the active control. However, those at clinics randomized to the intervention will be offered treatments for OUD that are known to be clinical effective.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Although the population enrolled in this Effectiveness trial is at high risk for adverse outcomes, the increased risk of participating in this study is minimal. The importance of the knowledge gained potential clinical benefit to study participants justifies the additional risk faced by study participants.

The psychological distress associated with survey questions will be mitigated by being able to skip any questions that participants are not comfortable with.

The possible loss of privacy is mitigated by keeping the answers to the survey questions strictly confidential. Survey data will be stored on a secure computer at the University of Washington and will only be available to the study team. The data will be stored and eventually destroyed in compliance with the University of Washington's data policies.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
Objective: Compare patient-reported outcomes in the intervention and control groups. **Hypothesis a:** *Compared to patients with MHS and OUD at clinics randomized to the control, patients at clinics randomized to the intervention group will have better patient-reported outcomes.* **Hypothesis b:** *Persistent use of MOUD will completely mediate any improvements in patient-reported outcomes observed in intervention clinics compared to control clinics.*	***Primary endpoint-*** *Self-reported opioid use, and self-reported mental health functioning* ***Secondary endpoints-*** *Persistent use of MOUD from PMID and self-report, disorder specific mental health symptoms (depression, anxiety and PTSD), self-reported access to OUD treatment, risk factors for premature mortality*
Secondary	
Objective: Compare the Detection of OUD pre- versus post-OUD screening implementation. **Hypothesis:** *The proportion of patients enrolled in the clinic with a MHD diagnosis and a new OUD diagnosis documented in the electronic medical record will be higher in the post-period than the pre-period.*	***Secondary endpoint*** *- the proportion of patients in the pre-screening sample with a new OUD diagnosis divided by the proportion of patients in the post-screening sample with a new OUD diagnosis*
Tertiary/Exploratory	
Objective: To conduct a pre-post evaluation (quantitative and qualitative) of a high-intensity sustainability implementation strategy delivered to the CHAMP intervention clinics to sustain the implementation of Collaborative Care for OUD co-occurring with MHD. **Exploratory Hypothesis:** *CHAMP intervention clinics receiving the high-intensity sustainability implementation strategy will maintain their implementation outcomes (adoption, reach, intervention fidelity and effectiveness) after the effectiveness trial has been completed (post) compared to during the effectiveness trial (pre).*	***Exploratory Endpoints –*** *Reach (number of patients engaged in the intervention)* *Adoption (number of providers delivering the intervention)* *Effectiveness (symptom change)* *Implementation fidelity (adherence to intervention protocols)*

4 STUDY DESIGN

4.1 OVERALL DESIGN

Overall Design

This multi-site study involves a sequence of trials (Pre-Post -> Effectiveness -> Implementation 3) to examine our primary, secondary and exploratory objectives.

1. Pre-Post trial (secondary objective) **-** Screening for OUD will be integrated into MHD screening and electronic health record (EHR) data will be used to determine if screening improves the detection of new cases of OUD during the first six months of the trial compared to the six months prior.

2. Cl*uster randomized Effectiveness trial (*primary objective) - The primary objective of the trial is to test the effectiveness of delivering MOUD in the context of CoCM for MHS, hereafter termed the "intervention" compared to CoCM for MHS only hereafter termed the "control". After monitoring CoCM for MHS fidelity during a three month "run in" phase, we will categorize clinics into one of two cohorts and then randomize them.

- **Cohort 1 (n=600) -** Randomize clinics with high CoCM for MHS fidelity to sequentially adding MOUD for OUD (intervention group) or maintenance CoCM for MHS only (control group).
- **Cohort 2 (n=600) -** Randomize clinics with low CoCM for MHS fidelity to simultaneous implementation of CoCM for MHS and OUD (intervention group) or CoCM for MHS only (control group).

3. ***Pre-Post Sustainability Evaluation*** **(exploratory objective) -** At the end of the Effectiveness trial, participating intervention clinics will receive a high-intensity implementation strategy to promote sustainability

Specific Aims and Hypotheses

Specific Aim 1 (Secondary Objective): Diagnostic data from electronic health records will be used to compare the detection of OUD pre-versus post-OUD screening implementation.

> **Hypothesis 1:** *The proportion of patients enrolled in the clinic with a MH diagnosis and a new OUD diagnosis documented in the electronic medical record will be higher in the post-period than the pre-period.*

Specific Aim 2 (Primary Objective): Patient reported outcomes will be analyzed to compare the effectiveness of the intervention versus the control.

> **Hypothesis 2a:** *Compared to patients with MHS and OUD at clinics randomized to the control group, patients at clinics randomized to the intervention group (both Cohorts 1 and 2) will report better access to and engagement in OUD treatment, less opioid use (primary outcome), better mental health*

functioning (primary outcome), fewer disorder specific mental health symptoms, better quality of life, and fewer risk factors for premature mortality.

Hypothesis 2b: *Engagement in MOUD (e.g., buprenorphine initiation and adherence) will completely mediate any improvements in patient reported outcomes observed in intervention clinics compared to control clinics.*

Specific Aim 3 (Exploratory Objective): To conduct a pre-post evaluation (quantitative and qualitative) of a high-intensity sustainability implementation strategy delivered to the CHAMP intervention clinics to sustain the implementation of Collaborative Care for OUD co-occurring with MHD.

Exploratory Hypothesis 3: *CHAMP intervention clinics receiving the high-intensity sustainability implementation strategy will maintain their implementation outcomes (adoption, reach, intervention fidelity and effectiveness) after the effectiveness trial has been completed (post) compared to during the effectiveness trial (pre).*

Randomization

Effectiveness Trial Randomization into Arms – Twenty-four clinics will be stratified according to fidelity cohort and healthcare organization and then randomized in a 1:1 ratio by our statistician into one of two arms (intervention or control). The intervention group is *CoCM for OUD and MHS*. The control group is *CoCM for MHS only*. Stratification serves two purposes. First, stratifying on healthcare organization (each has 2 or 4 clinics in the study) should balance the intervention and control groups according to key system level factors that influence quality and outcomes (e.g., EHR).[48] Second, stratifying on cohort ensures balance with regard to fidelity to the CoCM model which is likely to be correlated with our primary outcomes.

Rationale for Control Groups

Effectiveness Trial Control Group – The *CoCM for MHS only* was chosen as the control group because it represents high quality usual care. It is an active control. In addition, an active control is specified as the comparator because it would be unethical for patients with a life-threatening illness to be randomized to a treatment that is known to be ineffective.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The active control condition is CoCM for MHSs, but not OUD. CoCM for MHSs is now a reimbursable service and is being widely adopted in primary care clinics. Therefore, this control group represents high quality usual care. The evidence base clearly indicates that CoCM is effective for treating mild to moderate MHSs like depression and anxiety. Patient with more severe MHSs or addiction disorders are typically referred to specialty care. However, there is growing evidence that CoCM can also be used to treat more complex psychiatric disorders like PTSD. It is unknown whether CoCM can be used to effectively managed OUD, hence the scientific justification for the CHAMP study.

4.3 JUSTIFICATION FOR INTERVENTION

As noted above, it is unknown whether CoCM can be used to effectively managed OUD. Given the co-occurrence of MHS and OUD, testing an intervention which addresses both is critical. Furthermore, providing this treatment in primary care settings using a CoCM model will investigate the question of how to make high quality OUD treatment more available to patients.

4.4 END-OF-STUDY DEFINITION

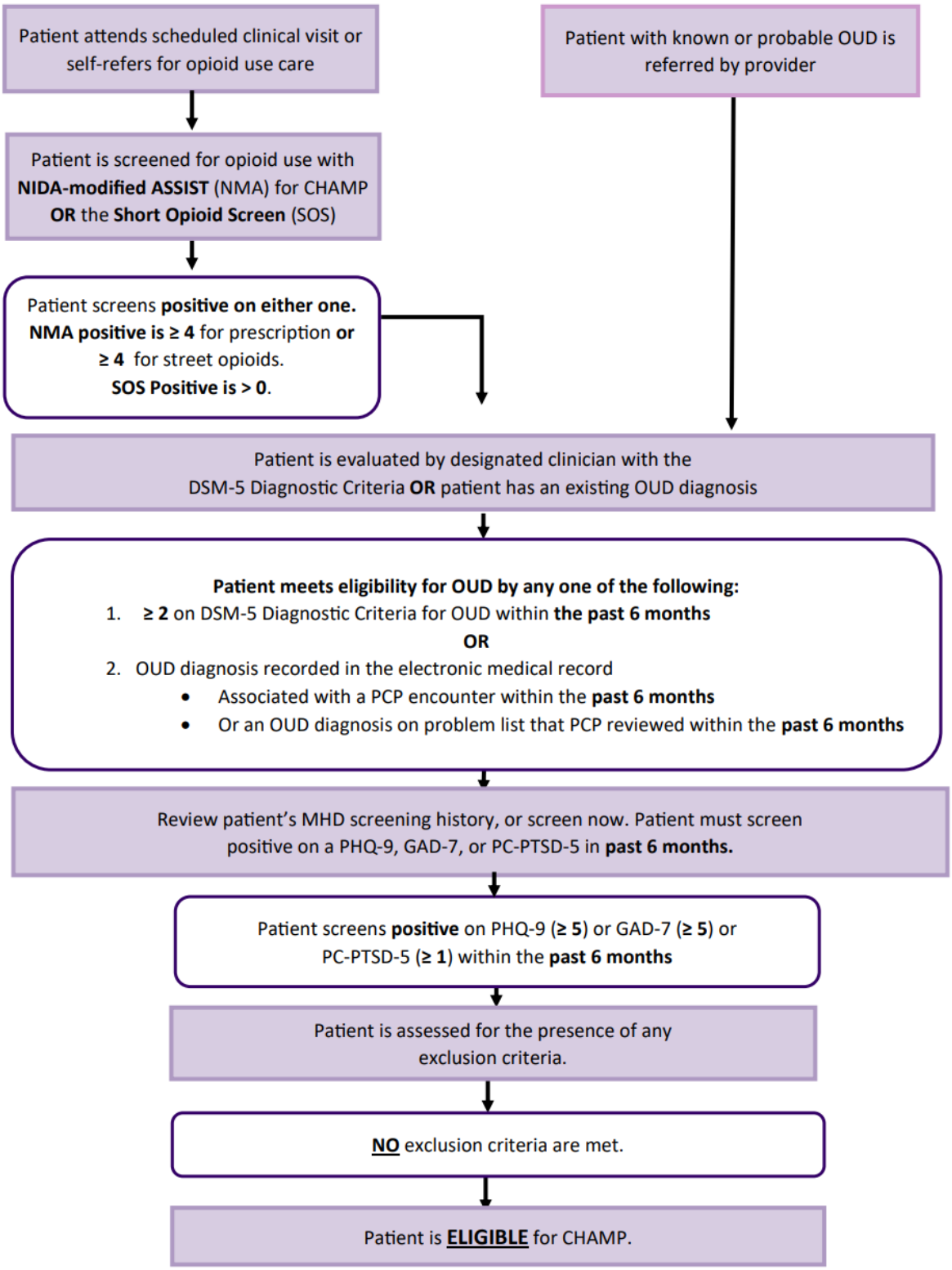
The end of study is defined as the last participant completing the 6-month follow-up survey.

5 STUDY POPULATION

The following graphic depicts patients enrollment in the Effectiveness trial along with the inclusion criteria. Stakeholders will be also recruited for qualitative interviews to support and evaluate implementation efforts. Stakeholders will also be recruited for qualitative interviews to evaluate sustainability efforts for the Implementation trial.

CHAMP Patient Eligibility Workflow

Revised—7.6.2021



5.1 INCLUSION CRITERIA

In order for patients to be eligible to participate in the Effectiveness trial, they must meet all of the following criteria:

1. Screen positive on the NIDA-Modified ASSIST OUD items OR the Short Opioid Screen (SOS) OR referred to the trial by one of the clinic's providers AND
2. Meet clinical criteria for ≥2 symptoms of OUD on the DSM-5 checklist (administered by a clinician) AND/OR OUD diagnosis recorded in the electronic medical record AND a patient encounter in the last 6 months OR OUD diagnosis on problem list PCP reviewed in the last 6 months.
3. Screen positive for depression on the PHQ-9 (≥ 5) OR generalized anxiety on the GAD-7 (≥ 5) OR PTSD on the PC-PTSD-5 (≥ 1) within past 6 months.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patient prefers, or is currently being prescribed psychotropic medication (including MOUD) by a Mental Health Care Specialist or board certified Addiction Medicine Specialist*. (NOTE: it is acceptable if the addiction specialist is a primary care provider in your clinic or health system)*
2. Patient is currently in, or is planning on entering a federally licensed opioid treatment program (i.e. methadone treatment program*) (NOTE: if patient actually does not enter an opioid treatment program or is later discharged from an opioid treatment program, patient could then become eligible)*.
3. Patient is currently in, or is planning on entering a specialty substance use disorders treatment program *(NOTE: If patient actually does not enter a residential treatment program or is later discharged from a residential treatment program, patient could then become eligible).*
4. Patient enrolled in CoCM for MHS and OUD for more than 14 days *(NOTE: relevant to intervention clinics only)*
5. Patient does not speak English or Spanish
6. Patient is younger than 18 years of age
7. Patient has a diagnosis of dementia
8. Patient lacks the capacity to provide informed consent
9. Patient does not plan on getting care at the clinic for the next 6 months.

For stakeholders to participate in the qualitative interviews to support and evaluate implementation of the intervention (CoCM for OUD and MHS), they must have been involved in the intervention either as a patient, provider or administrator in the past three months.

5.3 SCREEN FAILURES

Patients who are consented, but do not meet inclusion and exclusion criteria, will be withdrawn from the trial by the PI.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment will occur at 42 clinics and enrollment of women and minorities will reflect the underlying epidemiology of OUD in the clinical populations. We will enroll 1,200 patients during the course of the trial over a 33-month period (<2 patients per month).

As a quality improvement initiative, all clinics will implement universal screening for OUD. Screening procedures will follow those already in place of depression (PHQ-9) and other substance use and mental health disorders. Universal screening will identify undetected cases of OUD and support enrollment. Universal screening for OUD is a quality improvement activity that the clinics agreed to implement in order to be able to participate in the trial. The U.S. Preventive Services Task Force recommends screening for drug use in adults when services for accurate diagnosis, effective treatment, and appropriate care can be offered or referred.[49]

All participating clinics will identify staff to be trained in human subject's protection and designated to obtain informed consent. Having local staff recruit and consent will support enrollment.

If recruitment is lagging in the first six months, we will actively seek referrals from hospitals, emergency rooms or other community agencies serving people with OUDs/MHSs. We could also add more clinics (in randomized pairs) from the participating healthcare systems (see letters of support).

Patients will receive incentives to complete surveys and this remuneration increases with each subsequent survey, staring at $50 for the baseline and increasing to $50 for the 3-month follow-up and $50 for the 6-month follow-up as an incentive to complete all three surveys.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

*As described in **Section 2.2 Background**, CoCM is a stepped care model, and the intensity of treatment is determined by the needs of the patient and is therefore variable (i.e., there is no fixed number or duration for interventions contacts). Study participants in both arms of the study will be offered enrollment in the CoCM, but engagement is not required for the participant to contribute data to the evaluation.*

Table 1 – Description of CoCM Fundamental Principles and MOUD Core Components		
CoCM Principles	**Intervention**	
	Control Group	**Additions for Intervention Group**

Team Based: A team of providers working together using a shared care plan	• Prepared, proactive primary care practice
	• Minimum three-person CoCM team
	  ○ PCP diagnoses MH disorders
	  ○ PCP prescribes psychotropic medications
	  ○ CM provides care coordination
	  ○ Psychiatrist provides TX recommendations
	• Case reviews with CM and psychiatrist to discuss MHS
	• Clear communication strategies
	• Shared medical record
		• **Integration**
		  ○ Intervention team
		  ▪ PCP diagnoses OUD
		  ▪ Case reviews with CM and psychiatrist to discuss OUD
		  ▪ OUD TX included in shared medical record
		• **Pharmacological TX**
		  ○ PCP is waivered to prescribe MOUD
		  ○ PCP prescribes MOUD
		  ○ Psychiatrist is waived to prescribe MOUD

Patient-Centered: Shared decision making.	• Patient education
	  ○ Patients presented with both pharmacotherapy and psychotherapy TX options for MHS
	• Treatment preferences assessed
	• Shared decision making
	• TX and self-management goals set
	• Patient activation
		• **Pharmacological TX**
		  ○ Patients presented with pharmacotherapy TX options for OUD with emphasis that medication is essential for good outcomes
		  ▪ Transmucosal buprenorphine/Naloxone
		  ▪ Extended-release injectable buprenorphine
		  ▪ Extended-release injectable naltrexone
		• **Psychosocial**
		  ○ Patients presented with psychotherapy TX options for OUD

Population-Based: Tracking all patients proactively with a registry	• Track patients in registry
	• Use registry to proactively identify patients not engaged in care
	• Conduct outreach to patients falling through the cracks
		• **Pharmacological TX**
		  ○ CM tracks urine drug screen labs
		  ○ CM checks the state prescription drug monitoring program for prescription fills
		  ○ CM uses call back protocol to assess for medication diversion

Measurement-Based: Systematic use of clinical outcome measures to support treatment to target	• Screen for MHS using PHQ-9 and GAD-7, and PC-PTSD-5
	• Monitor symptoms over time with PHQ-9, GAD-7 and PCL-5
	• Identify patients not responding to TX
	• Intensify TX
	  ○ Switch/Augment psychotropic
	  ○ Augment with psychotherapy
	  ○ Refer for specialty mental health consultation
	  ○ Refer for specialty mental health TX
	  ○ Stepped care
		• **Integration**
		  ○ Screen for OUD using NIDA-ASSIST
		  ○ Screen for SUDs using AUDIT-C and BAM
		• **Pharmacological TX**
		  ○ Monitor OUD patients
		  ▪ Opioid withdrawal symptoms
		  ▪ Illicit opioid craving
		  ▪ Illicit opioid use
		  ▪ Medication side effects
		  ▪ Urine drug screens
		  ○ Identify patients not responding to treatment
		  ○ Intensify TX
		  ▪ Switch/Augment OUD medications
		  ▪ Augment with psychotherapy
		  ▪ Refer for specialty addiction consultation
		  ▪ Refer for specialty addiction TX
		  ▪ Stepped care

Evidence-Based: Delivery of evidence-based psychosocial and pharmacological treatments	• Deliver high fidelity evidence-based psychotherapy for MHS
	  ○ Behavioral Activation
	• Prescribe evidence-based psychotropic medications for MHS
	  ○ Side effect management
	  ○ Address adherence barriers
		• **Psychosocial**
		  ○ Deliver high fidelity evidence-based psychotherapy for OUDs
		  ▪ Behavioral Activation for SUD
		  ○ Encourage attendance at mutual help groups
		• **Pharmacological TX**
		  ○ Prescribe MOUD for OUD

	• Conduct suicide risk assessment and safety planning
	• OUD Treatment Options
	  ○ Refer to specialty addiction treatment for OUD
	  ○ SAMHSA Providers Clinical Support System (MPI Saxon – Mentor)	

Accountable: The team and the health care organization monitor process and outcome measures and conduct QI activities	• Specify process of care and outcome metrics for MHS
	• Set metric benchmarks for MHS
	• Monitor MHS metrics for providers and clinics
	• Conduct QI for any lower than expected performance on MHS metrics
		• **Integration**
		  ○ Specify process of care and outcome metrics for OUD
		  ○ Set metric benchmarks for OUD
		  ○ Monitor OUD metrics for providers and clinics
		  ○ Conduct QI for any lower than expected performance on OUD metrics
		  ○ Monitoring to meet regulatory requirements for buprenorphine/naloxone prescribing

Abbreviations: PCP – Primary Care Providers, CM – Care Manager, TX – Treatment, QI – Quality improvement, SAMHSA - Substance Abuse and Mental Health Services Administration, MHS – Mental Health Symptoms, OUD – Opioid Use Disorder, SUD – Substance Use Disorder.

Intervention

Based on a recent evidence synthesis,[50] MOUD has three core components: 1) integration of OUD treatment with other MHS and physical health disorders, 2) pharmacological treatment, and 3) psychosocial support.[50] Table 1 describes the core components of the intervention and the active control. Primary care providers will provide all psychotropic and MOUD medications with consultation from a psychiatrist and support from a care manager. Care managers monitor symptom response using structured instruments and provide behavioral activation. In contrast to the control group, care managers in the intervention group specifically monitor OUD outcomes and the behavioral activation will focus on opioid addiction. Primary care providers in the intervention group will be waivered and expected to prescribe MOUD. Primary care providers in the control group will also be allowed to be waivered and prescribe MOUD.

Mechanism of Action – The hypothesized mechanism of action is MOUD persistence defined as the ratio of the number of days they reported taking the MOUD medication (numerator) to the number of days during the 6-month follow-up period for which it was prescribed (denominator).[51]

Integrated Treatment – The treatment of OUD will be integrated with the treatment of MHS, other substance use disorders (SUDs), and physical health disorders. **Team-Based:** The integrated care team will include a care manager, primary care providers and consulting psychiatrist. Consulting psychiatrists will have a buprenorphine waiver and be trained by MPI Saxon. **Patient-Centered:** The care manager will educate, activate, promote self-management, assess treatment preferences, and engage in shared decision making. **Population-Based:** The care manager will enter patients in the CMTS registry and conduct outreach activities with those who miss appointments. **Measurement-Based:** OUD, other SUD, and MHS will be assessed over time and stored in CMTS. Care managers will use the PHQ-9 for depression, the GAD-7 for anxiety and the PCL-5 for posttraumatic stress disorder (PTSD). For patients not experiencing a 50% decrease in symptom severity, options for "*treating to target*" include: 1) increasing dose, 2) switching medications, 3) augmenting medications, and/or 4) intensifying psychosocial interventions. Treatment adherence and side effects will also be monitored and managed. Monitoring OUD symptoms and adherence is described below. **Evidence-based:** The primary care provider will prescribe FDA approved psychotropic medications for depression, anxiety and PTSD concurrently with pharmacologic treatment of OUD (as described below). Care managers will also be

trained to deliver Behavioral Activation (described below). For alcohol, the primary care provider will prescribe one of two FDA approved medications (disulfiram or acamprosate) that can be used with buprenorphine. The care manager will use the AUDIT-C[52] for measurement based care. For benzodiazepines, the care manager will screen for anxiety and sleep disorders, and if present the consulting psychiatrist will recommend a trial of an SSRI or trazodone. For other SUDs, we will deliver Behavioral Activation and encourage abstinence. Primary care providers will offer appropriate management of physical health disorders common among patients with OUD and MHS such as chronic obstructive pulmonary disease, viral hepatitis, human immunodeficiency virus, and chronic pain.

Pharmacological Treatment/MOUD - Pharmacologic treatment of OUD will rely mainly on transmucosal buprenorphine/naloxone prescribed by primary care providers with DATA 2000 waivers. Frequency of medication self-administration will be tailored for each patient (from 7 day to 30 day supply) based on regularity of appointment attendance, evidence of illicit substance use, and evidence of treatment adherence. Extended-release injectable buprenorphine will also be available for patients with inadequate medication adherence. Some selected patients who agree to complete opioid withdrawal and prefer antagonist treatment can receive extended-release injectable naltrexone. Methadone will not be used because it cannot be prescribed in the primary care setting. Referral to federally licensed opioid treatment programs that dispense methadone will be an option if needed. **Measurement-Based:** Though no studies to our knowledge have used measurement-based care to support OUD treatment, measurement-based care and "*treat to target*" are fundamental principles of CoCM and will be incorporated into the intervention. Care managers will ask four yes/no questions about: 1) opioid withdrawal symptoms, 2) illicit opioid craving, 3) illicit opioid use, 4) medication side effects. Whenever possible, we will corroborate negative self-reports of illicit opioid use with urine drug screens. In addition, care managers will ask patients about medication adherence to make sure patients are taking the medication as prescribed and not waiting for withdrawal symptoms, swallowing the transmucosal medication, or smoking/eating before taking the medication. Self-reported adherence will be corroborated by regular checking of the state prescription drug monitoring program to assure that patients are picking the medication up from the pharmacy. To monitor for medication diversion, we will use a call-back protocol developed by MPI Saxon and colleagues.[53] All patients will be told about the call-back protocol (as a prevention intervention), but the protocol will only be used when clinically indicated. If called back, patients will be asked to return to the clinic within 24 hours with their MOUD medication supply. If the pill count is short, medication diversion will be presumed, and the patient will be switched to injectable buprenorphine if possible or limited to a 7 day supply. **Treatment to Target:** If the patient is experiencing opioid withdrawal symptoms, illicit opioid craving, or illicit opioid use, the care manager will alert the consulting psychiatrist during the case review. The consulting psychiatrist will then *recommend* a change to the treatment plan to the primary care provider. In the case of buprenorphine/naloxone, options for changing the treatment plan include: 1) increasing the dosage (max dose 32mg), 2) augmenting with clonidine,[54] 3) switching to injectable buprenorphine, and/or 4) intensifying psychosocial interventions. If the patient is experiencing medication side effects, but not opioid withdrawal symptoms or illicit opioid craving, consideration will be given to lowering the medication dosage. In the case of extended-release naltrexone, only a single dosage is available, so options include: 1) switching to buprenorphine/ naloxone, 2) augmenting with clonidine, and/or 3) intensifying psychosocial interventions.

Psychosocial Support - Psychosocial support will be provided by the care manager under the guidance of the consulting psychiatrist. Care managers will be trained by Co-I Simpson to deliver behavioral activation (BA), an established psychosocial intervention for depression and anxiety, and an emerging intervention for PTSD,[55-57] OUD,[58,59], and other SUDs.[60] BA is a brief and relatively simple therapy that can be delivered by mid-level providers. BA benefits patients with OUD and comorbid MHS because it

helps to counter behavioral avoidance by assisting patients in identifying valued activities and developing strategies for pursuing them in healthy, non-drug use ways. Additionally, because individuals with OUD and comorbid MHS often neglect important aspects of their lives (e.g., wellness and financial obligations), BA is well-suited to helping them systematically address these problems that if left unaddressed are risk factors for relapse. Importantly, use of non-opioid psychoactive substances, including alcohol, will be monitored and addressed in the context of BA treatment as needed.[60] We will also use BA to assist patients in identifying and engaging family and friends who are supportive of their recovery efforts.[61] This component will also include gentle encouragement to attend mutual help groups such as Narcotics Anonymous. Receipt of specific BA elements will be tracked at the encounter level in the CMTS registry.

Control

The active control will provide integrated treatment for MHS described above, but not treat OUD. Treatment for OUD will involve referral to specialty settings.

6.1.2 ADMINISTRATION AND/OR DOSING

Providers – Providers include the patients regular primary care provider, their assigned care manager and the psychiatric consultant. All providers are routine care staff at the participating clinics.

Care Management Tracking System (CMTS) – For the evaluation, CMTS will be used to measure the number of care manager encounters, the number of care manager encounters with recorded elements of BA, number of psychiatric case reviews, urine test results, medications prescribed for OUD and MHS, as well as results of state prescription drug monitoring checks to obtain an objective measure of MOUD initiation and adherence. For injectable buprenorphine or naltrexone, clinic staff will likewise record the administration of these injections in the CMTS.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Intervention *fidelity* will play a critical role in this study. If fidelity is artificially controlled, the trial would lack external validity.[62] If fidelity is poor, we would run the risk of incorrectly concluding that the potential clinical effectiveness of the intervention is not better than the control. Therefore, we will take a *balanced* approach whereby the implementation team will monitor fidelity and use real-world implementation strategies to ensure that each clinic achieves and maintains a sufficient level of fidelity required for the intervention to *potentially* be clinically effective. *External facilitation*[63,64] will be used to deliver a combination of implementation strategies that the AIMS Center has practice-tested and refined over the years. These implementation strategies are known to be effective for CoCM for MHS[65], and thus will not be evaluated. For the 12 clinics randomized to implement the intervention *only*, we will conduct an ongoing mixed methods *formative evaluation* to assess implementation success, identify emergent barriers and tailor implementation strategies to improve fidelity. Implementation fidelity will be measured using the intervention fidelity rubric and process measures available in the CMTS registry (e.g., % of patients with regular care manager contacts and psychiatric case reviews).

The AIMS Center has an established implementation approach that includes *training* and *external facilitation* to support practice change required to implement CoCM. Each practice will identify a clinic implementation team, comprised of clinic managers, primary care provider champions, and practice/program managers. Additional team members can include clinic leaders, psychiatric consultant, care manager, and finance/compliance officers. In the **Exploration** phase, the clinic implementation team develops a shared vision, business plan and rationale for undertaking the CoCM practice change including consideration of the *Outer Setting*, *Inner Setting*, and *Intervention Fit* with current clinical capacities and workflow. In the **Preparation** phase, the clinic implementation team focuses on developing clear workflows to deliver the six CoCM fundamental principles. The CoCM/CHAMP team members all complete basic training on CoCM/CHAMP role responsibilities and role specific didactics such as BA training for the care manager or MOUD training/waiver for the primary care provider. During the **Implementation** phase, external facilitation supports the CoCM/CHAMP team to meet process and outcome benchmarks. Role specific learning communities are established to promote adaptations of skills to deliver patient care as a team.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The Effectiveness and Implementation trials use cluster (site-level) randomization. Sites will be stratified by fidelity and healthcare organization prior to randomization. Those administering the surveys to patients will be masked to randomization status (and site). If survey administrators are inadvertently unmasked, that will be recorded and the rate of unmasking will be monitored. The analysis will examine the potential for bias as a result of making.

Study Multiple PIs will not have access to survey data until the last patient has completed the 6-month follow-up survey. The study statisticians and data analysts will have access to survey data, adverse events and randomization status to generate reports for DSMB meetings.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Patient adherence is not required for participation in the Effectiveness trial. Patient engagement in MOUD is hypothesized as the clinical Mechanism of Action. Patient self-report will be used to determine whether the patient engaged in MOUD, defined as the ratio of the number of days they reported taking the MOUD medication (numerator) to the number of days during the 6-month follow-up period for which it was prescribed (denominator).

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

Stopping the Effectiveness Trial – All medications for OUD and MHS are FDA approved, and the BA psychotherapy has been demonstrated to be effective in numerous RCTs. Therefore, we are not specifying any criteria for suspending or stopping the Effectiveness trial (intervention or evaluation). The

DSMB will review reports about enrollment, adverse events, protocol implementation, and data quality at their meetings and could decide to discontinue the Effectiveness trial.

Discontinuing Treatment – The clinic providers can choose to initiate or discontinue any OUD or MHS treatment at any time during the Effectiveness trial. In this case, the patient would remain enrolled in the study for evaluation purposes. Study participants may also refuse or discontinue treatment at any time during the Effectiveness trial and will remain enrolled in the study for evaluation purposes.

Refusing to Participate in the Evaluation – Study participants may refuse to complete the surveys. Survey refusers will remain in the Effectiveness trial and may continue to receive CoCM for OUD and/or MHS (contributing CMTS data).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Patient Requests Study Withdrawal – If a study participant writes to the PI stating that they would like to withdraw from the Effectiveness trial, we will stop collecting survey data and we will not use CMTS data for evaluation purposes after that date. Patients withdrawing from the Effectiveness trial may continue to receive CoCM for OUD and/or MHS or decline further treatment.

PI Withdraws Patient from Study – A PI may terminate a enrollee's participation in the Effectiveness trial for the following reasons:

- The PI learned that the study participant did not meet inclusion criteria or did meet exclusion criteria at the time of enrollment.
- Other unanticipated reasons

Patients withdrawn from the study by the PI may continue to receive CoCM for OUD and/or MHS.

7.3 LOST TO FOLLOW-UP

Definition of Lost to Follow-Up – A study participant will be considered to have been lost to follow-up by the survey team if it has been more than 14 days after the baseline survey was scheduled to be completed or more than 30 days after the 3-month or 6-month follow-up survey was scheduled to be completed.

Retention – Study participants will be able to complete the survey on the phone or on the web. Consenting patients will be asked to provide at least four alternative contacts, in addition to their own telephone number and email address, and to agree for us to contact these alternates if we lose touch with the patient. In addition, to mailing reminders about completing the follow-up surveys, we will also request permission from patients to text and/or email them reminders with a link to the web-based survey. We will identify ourselves as representing the primary care clinic but will not disclose any other details about the purpose for trying to reach the participant. Clinics will be alerted if the data collection team loses touch with the patient and asked to flag the registry so the patient can provide updated contact information at their next visit to the clinic. Patients will receive incentives to complete surveys and this remuneration increases with each subsequent survey.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Screening and Eligibility Assessment – To be enrolled/consented in the Effectiveness trial, a patient must have screened positive for OUD and a MHS in the past six months AND currently meet clinical criteria for ≥2 symptoms of OUD on the DSM-5 checklist *AND/OR OUD diagnosis recorded in the electronic medical record AND a patient encounter in the last 6 months OR OUD diagnosis on problem list PCP reviewed in the last 6 months.*

Survey Administration – Surveys will be administered at baseline, and at 3- and 6-month follow-ups.

Construct/Instrument	**Baseline**	**3-Month Follow-Up**	**6-Month Follow-Up**
Demographics	X		
Social Determinants	X		
Homelessness Screening Clinical Reminder	X		
Legal involvement question (Addiction Severity Index – modified)	X		
Insurance	X		
Pain (PEG)	X	X	X
Alcohol Use (AUDIT)	X	X	X
Opiate Use (BAM-R)	X	X	X
Opiate Craving Question (Addiction Severity Index – modified)	X	X	X
Readiness to Change (ICR)	X		
Other Drug Use (BAM- R)	X	X	X
Recent Experience of Overdose	X	X	X
Health Related Quality of Life (Veterans Short Form-12)	X	X	X
Depression (SCL20)	X	X	X
Anxiety (Neuro-QOL Measure - Anxiety, Short Form)	X	X	X
Trauma (PC-PTSD-5 Criteria A screener)	X	X	X
PTSD (PCL-5)	X	X	X
Access to Care (SPIRIT Perceived Access Inventory)	X	X	X
Service Utilization	X	X	X
Medication Use	X	X	X
Side Effects	X	X	X

Care Management Tracking System (CMTS) – After the last study participant has completed the 6-month follow-up, we will extract information from CMTS. CMTS is a web-based registry hosted by the AIMS Center and used by the care managers to track process and outcomes.[20] The CMTS contains clinic-level process of care and patient-level clinical outcome data that shows how patients receive care. For the evaluation, CMTS will be used to measure the number of care manager encounters, the number of

care manager encounters with recorded elements of BA, number of psychiatric case reviews, urine test results, medications prescribed for OUD and MHS, as well as results of state prescription drug monitoring checks to obtain an objective measure of MOUD initiation and adherence. For injectable buprenorphine or naltrexone, clinic staff will likewise record the administration of these injections in the CMTS.

8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.2.1 DEFINITION OF ADVERSE EVENTS

Definition of an Adverse Events: Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or lab finding), symptom, or disease temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

We will report the following Adverse Events:

01. Non-suicidal self-injury that did not result in Hospitalization or ED Visit
02. Other_____

Adverse Events will be classified as serious or non-serious; expected or unexpected; and as definitely study-related, probably study-related, possibly study-related, or definitely not study-related.

8.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS

Definition of a Serious Adverse Events: Any adverse event temporally associated with the subject's participation in research that is potentially life threatening, results in death, requires hospitalization, results in persistent or significant disability/incapacity, or any other adverse event that, based upon appropriate medical judgment, may jeopardize the medical or surgical intervention to prevent one of the other outcomes listed here.

We will report the following Serious Adverse Events:

01. Suicide attempt
02. Suicide resulting in death
03. Death (not suicide or unsure if suicide)
04. Non-suicidal self-injury that resulted in Hospitalization
05. Non-suicidal self-injury that resulted in ED Visit
06. Non-lethal overdose (that resulted in hospitalization or ED visit)
07. Non-lethal overdose (that did not result in hospitalization or ED visit)06. Hospitalization (not due to suicide attempt or non-suicidal self injury)
07 ED Visit (not due to suicide attempt or non-suicidal self injury)
08. Non-lethal Overdose (with no hospitalization or ED visit)
09. Serious Medication Reaction (that resulted in a clinical encounter)
10. Other: _____

Serious Adverse Events will be classified as expected or unexpected; and as definitely study-related, probably study-related, possibly study-related, or definitely not study-related.

8.2.3 CLASSIFICATION OF AN ADVERSE EVENT

8.2.3.1 SEVERITY OF EVENT

Adverse Events will be considered either serious or non-serious based on the definition of Serious Adverse Event Above.

8.2.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All Adverse Events and Serious Adverse Events will be classified as:

01 - Definitely study related (100%)

There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The event must be pharmacologically or phenomenologically definitive.

02 - Probably study related (50-99%)

There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals.

03 - Possibly study related (1-49%)

There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an adverse event may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

04 - Definitely not study related (0%)

The event is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3.3 EXPECTEDNESS

There are numerous risks that are anticipated for this population of patient with OUD and comorbid MHS. These risks are both study-related and non-study-related.

Anticipated study-related risks associated with evaluation activities include:

01 psychological distress due to survey questions
02 potential loss of confidentiality

Study participants in both the intervention and control groups will be more likely to be started on FDA approved medications or have their dosages increased than non-study participants. Therefore, anticipated study-related risks associated with clinical activities include:

01 anticipated side-effects
02 opioid craving for those initiating MOUD.

Because of the severity and comorbidity of addiction and mental illness in our study population, it also anticipated that study participants will experience the following non-study related Adverse Events and Serious Adverse Events with a high degree of frequency:

01 Non-lethal self-harm (Adverse Event)
02 Suicide attempt (Serious Adverse Event)
03 Death by suicide (Serious Adverse Event)
04 Accidental overdose (Serious Adverse Event)
05 Emergency department visits and/or hospital admissions (Serious Adverse Event)

8.2.4 ADVERSE EVENT REPORTING

Event Type	Report To DSMB	Reporting Timeframe
Adverse Event	Summary Report	Annually
Unanticipated Problem	IRB Unanticipated Problem Report	Report within 10 business days
	NIMH Unanticipated Problem Report	Report within 10 business days
IRB Determination is Serious or Continuing Noncompliance	NIMH Noncompliance Report	Report within 10 business days of IRB determination
IRB Determination is Study Suspension or Termination	NIMH Study Suspension Report	Report within 3 business days of IRB determination
Protocol Deviation	Summary Report	Annually

8.2.5 SERIOUS ADVERSE EVENT REPORTING

Event Type	Nature of Event	Study Related	Report To	Reporting Timeframe
Serious Adverse Event	Unexpected	The event is related	IRB Serious Adverse Event Report	Report within 10 business days

		(possibly, probably, definitely related) to the research	NIMH Serious Adverse Event Report	Report within 10 business days
Serious Adverse Event	Expected	Related or Unrelated	DSMB	Report 3 times a year
Serious Adverse Event	The Nature of Event is: "Suicide resulting in death" **OR** "Death (not suicide or unsure if suicide)"	The death is related (possibly, probably, or definitely related) to the research	NIMH Death Report	Report no later than within 5 business days
Serious Adverse Event	The Nature of Event is: "Suicide resulting in death" **OR** "Death (not suicide or unsure if suicide)"	The death is definitely not related to the research	DSMB	Report 3 times per year

8.2.6 REPORTING EVENTS TO PARTICIPANTS

If our Single IRB determines that an Adverse Event or Serious Adverse Event needs to be reported to an individual study participant, one of the multiple PIs will telephone that person and notify them of the event and explain the risk. If our Single IRB determines than an Adverse Event or Serious Adverse Event needs to be reported to all study participants, notifications will be emailed and mailed to study participants.

8.3 UNANTICIPATED PROBLEMS, PROTOCOL DEVIATIONS, AND NON-COMPLIANCE

8.3.1 DEFINITION OF UNANTICIPATED PROBLEMS

Definitions

1. **Unanticipated Problems:**
    a. Unexpected in terms of nature, severity, or frequency, given 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 studies
b. Related or possibly related to a subject's participation in the research
c. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

2. **Protocol Deviation:** An accidental or unintentional change to the IRB-approved protocol that may cause harm to subjects or others, indicates that the subjects or others are at an increased risk of harm, or has adversely impacted data integrity. *Protocol deviations will be reported to the Single IRB as either an unanticipated problem or noncompliance.*

3. **Noncompliance:** any action or activity associated with the conduct or oversight of research involving human subjects that fails to comply with applicable regulations, the IRB's *Handbook*, and/or the determinations and requirements of the IRB. Noncompliance may range from minor to serious; be unintentional or willful; and may occur once, sporadically, or continuously.

    a. ***Serious Noncompliance:*** any action or omission in the conduct or oversight of research involving human subjects that affects the rights and welfare of subjects, increases risk to subjects, or compromises the scientific integrity or validity of the research.

    b. ***Continuing Noncompliance:*** a pattern of repeatedly failing to comply with applicable regulations, the IRB's Handbook, and/or the determinations and requirements of the IRB that may affect subjects' rights and welfare, increase risk to subjects, or may compromise the scientific integrity or validity of the research. Continuing noncompliance also includes frequent instances of minor noncompliance or failure to respond to a request to resolve an episode of noncompliance.

8.3.2 PROBLEM REPORTING

Unanticipated problems, protocol deviations, or instances of non-compliance will be reported to our Single IRB within 10 business days, along with any corrective actions that have been or will be taken. Our Single IRB will determine whether an unanticipated problem, protocol deviation, or instance of non-compliance needs to be reported to an individual or to all study participants. All Unanticipated Problems, protocol deviations, or instances of non-compliance will be compiled and reported to the NIMH DSMB as per the adverse event reporting table above.

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations to the Single IRB. As specified in **Section 8.3.5, Adverse Event Reporting,** the PIs will report protocol deviations to the Single IRB that are considered to be *unanticipated problems* or *noncompliance* within 10 business days. The PI will be responsible for knowing and adhering to any actions required by the Single IRB, including modifying the protocol and/or report to the NIMH and the NIMH DSMB, as noted in the event reporting table above.

8.3.3 REPORTING PROBLEMS TO PARTICIPANTS

If our Single IRB determines that an unanticipated problem, protocol deviation, or instance of non-compliance needs to be reported to an individual study participant, will telephone that person and notify them of the event and explain the risk. If our Single IRB determines than an unanticipated problem, protocol deviation, or instance of non-compliance needs to be reported to all study participants, notifications will be emailed and mailed to study participants.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Hypotheses for Primary Objective (Effectiveness Trial)

Hypothesis a: *Compared to patients with MHS and OUD at clinics randomized to the control, patients at clinics randomized to the intervention group (both Cohorts 1 and 2) will report better access to and engagement in OUD treatment, less opioid use (primary outcome), better mental health functioning (primary outcome), fewer disorder specific mental health symptoms, better quality of life, and fewer risk factors for premature mortality.*

Hypothesis b: *Engagement in MOUD will completely mediate any improvements in patient reported outcomes observed in intervention clinics compared to control clinics.*

Hypothesis for Secondary Objective (Pre-Post Trial)

Hypothesis: *The proportion of patients enrolled in the clinic with a MH diagnosis and a new OUD diagnosis documented in the electronic medical record will be higher in the post-period than the pre-period.*

Exploratory Hypothesis for Exploratory Objective (Pre-post evaluation)

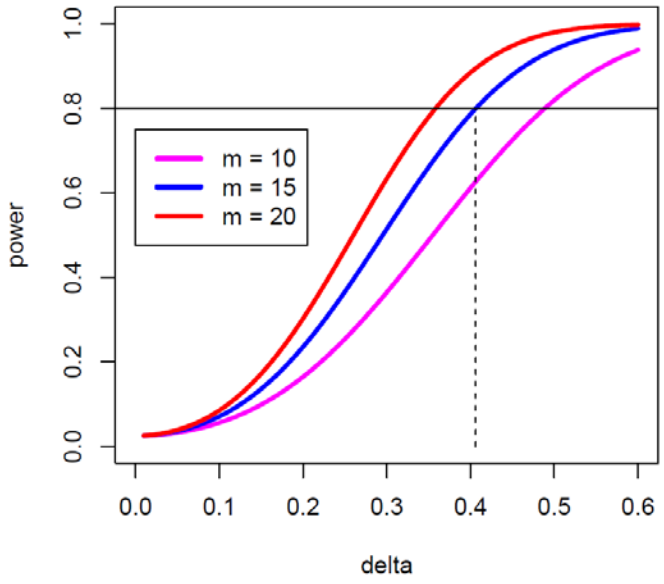
Exploratory Hypothesis : *CHAMP intervention clinics receiving the high-intensity sustainability implementation strategy will maintain their implementation outcomes (adoption, reach, intervention fidelity and effectiveness) after the effectiveness trial has been completed (post) compared to during the effectiveness trial (pre).*

9.2 SAMPLE SIZE DETERMINATION

Power Analysis For Pre-Post Trial – Under the assumption of 24 clinics, at least 500 eligible MHS patients in each clinic in each six-month period, a rate of documented OUD of 1% pre-screening, a conservative estimate of 0 correlation between pre- and post-percentages, and an alpha significance level of 0.05, we will have 80% power to detect an increase from a pre-screening percentage of 1% to a post-period percentage of 1.7%.

Power Analysis For Effectiveness Trial - Assuming a coefficient of variation of 0.33 for the continuous outcome of days of illicit opioid use[676] and SF12V MCS scores[6687], a highly conservative intraclass correlation within clinics of 0.03, 12 clinics per group and 40 patients per clinic (n=960, accounting for

20% attrition), we will have 80% power to detect an effect size of 0.31. We chose to use a highly conservative intraclass correlation to ensure sufficient power for secondary outcomes and mediation analyses (Hypothesis 2b). Thus, conservatively we will have 80% power to detect a 10 % difference in number of days using illegal opioids in the past month (e.g., 15.00 days compared to 13.5 days) and 10% difference in MCS scores (e.g., 40 compared to 36) between CHAMP and CoCM for MHS only clinics. Because these are multiple primary outcomes (and not co-primary outcomes), this power analysis assumes a Bonferroni correction for the two multiple primary outcomes. Specifically, the intervention will be interpreted to have been successful if there is a significance group different between either primary outcome, not both primary outcomes. Because of recruitment challenges, power analyses are also now provided for the lower bounds of expected enrollment. The lower-bounds power analysis assumes that we will recruit 360 study participants instead of 1200. For this lower-bounds power analysis, we assume a more realistic intraclass correlation of 0.01 instead of 0.03. Collaborative care trials conducted by Dr. Fortney (MPI) and Dr. Schoenbaum (NIMH collaborator) found intraclass correlation coefficients in the range of 0.008-0.001).[30,66] Assuming a coefficient of variation of 0.33 for the continuous outcome of days of illicit opioid use[67] and SF12V MCS scores[68], an intraclass correlation within clinics of 0.01, 12 clinics per group, 15 patients enrolled per clinic (n=288 accounting for 20% attrition), we will have 80% power to detect an effect size of 0.41. The sample size of 360 does not represent a revised enrollment target, and we will continue to enroll as many study participants as possible (up to 1,200) using enhanced recruitment methods and by extending the recruitment period if possible.



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9.3 POPULATIONS FOR ANALYSES

Intention-to-Treat

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Statistical Analysis Plan - There will be a formal Statistical Analysis Plan that will be completed prior to unblinding of the Effectiveness trial data. The statistical plan will be posted publicly or registered before the study begins.

Reporting of Descriptive Statistics – Categorical data collected at baseline will be presented as percentages. Continuous data will be presented as means with standard deviations.

Statistical Tests – An alpha level of 0.05 and two-tailed tests will be used to determine statistical significance.

Covariates – Covariates will be included if they are theoretically related to both the dependent variable and the probability of having missing data, and will be specified later in the SAP.

Test of Distributional Assumptions – We will examine residuals for normality. If residuals are not approximately normally distributed, we will use a sandwich estimator (e.g., robust maximum likelihood estimator) to correct standard errors. Note that the treatment effect is a binary indicator and consequently, the point estimate for treatment condition will be unbiased, conditional on other model effects being specified correctly. For continuous covariates, we will examine scatterplots and partial regression plots to ensure the linearity assumption is reasonable. If linearity appears to be meaningfully violated, we will transform either the predictor variables or the outcome, depending on the patterning of nonlinearity.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Primary Outcomes of Effectiveness Trial - The *multiple* primary outcomes evaluated will be patient-reported measures of illicit opioid use, and mental health functioning. *Opioid use* will be measured using item 7E from the Brief Addiction Monitor (BAM)[68]: *" In the past 30 days, how many days did you use opiates such as Heroin, Morphine, Dilaudid, Demerol, Oxycontin, oxy, codeine (e.g., Tylenol 2,3,4), Percocet, Vicodin, Fentanyl, etc.? Do not count times you used buprenorphine, suboxone, or methadone as directed by a healthcare provider."* Mental health functioning will be measured using the Mental Component Summary score of the SF-12.

Intent to Treat Analysis of Primary Outcomes of Effectiveness Trial – Given the cluster-randomization we will use appropriate mixed models (also known as multi-level models) to account for clinic effects that are shared by subjects from the same clinic. Measurement occasions (level 1) will be nested within individuals (level 2) which are then nested within clinics (level 3). All outcomes will be analyzed with a multilevel model accounting for clustering of observations (level 1) within patients (level 2) and clinics (level 3). The model will include a random intercept and random linear slope to account for person-level clustering and repeated measures on individual subjects over time that may be associated with variable time trends across participants. To allow for curvilinear change over time, time will be entered as a nominal variable by including dummy codes for the 3- and 6-month time points. The explanatory

variable of interest will be group randomization status (e.g., intervention versus control). Main effects and interaction terms with time-indicator variables capture the difference between intervention and control group at each wave. Covariates will be included if they are theoretically related to both the dependent variable and the probability of having missing data. An alpha level of 0.05 and two-tailed tests will be used to determine statistical significance. Results will be presented as adjusted differences between groups with confidence intervals. **Missing Data -** We will examine patterns of missing data to determine the degree to which the missing at random assumption (the degree to which missingness is related to variables included in the model) is plausible. With high missing rates, we may use missing data methods to account for missing not at random mechanisms. If warranted, multiple imputation or similar methods will be used to account for missing data on completed or partially completed baseline and follow-up surveys (e.g., skipped items).

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary Outcomes of Effectiveness Trial - The secondary outcomes are perceived access, quality of life and risk factors for premature mortality. *Access***:** Perceived access to OUD services will be measured using a modified version of the 9-item SPIRIT Perceived Access Scale developed for our PCORI trial. The scale is based on theory,[11] has excellent internal consistency (κ - 0.89), and concurrent validity with number of mental health encounters (p=0.016). *PTSD symptoms* will be assessed using the PCL-5.[69] *Depression symptoms* will be assessed using the SCL-20.[70] *Anxiety* will be measured using the Neuro-QOL Measure - *Emotional Distress, Anxiety, Short Form 7a*.[71,72] *Health Related Quality of Life* will be measured using the Veterans Short Form-12.[73] *Risk factors for premature mortality***:** Risks, including suicidal ideation (two items from SCL-20), discontinuing MOUD[6], overdose, suicide attempts, emergency department admission, hospitalization[74] and death, will be collected from participating clinics as part of the adverse event reporting process. Depending on their observed frequency, these risk factors will be analyzed separately or grouped.

Clinical Mechanism of Action (MOUD Persistence) - Patient self-report will be used to determine whether the patient engaged in MOUD, defined as the ratio of the number of days they reported taking the MOUD medication (numerator) to the number of days during the 6-month follow-up period for which it was prescribed (denominator).[51]

Intent to Treat Analysis of Secondary Outcomes and Clinical Mechanism of Action of Effectiveness Trial - Measurement occasions (level 1) will be nested within individuals (level 2) and nested within clinics (level 3). All outcomes will be analyzed with a multilevel model accounting for clustering of observations (level 1) within patients (level 2) and clinics (level 3). Regression models will be specified with the appropriate distribution and link functions to match the dependent variable (linear for the continuous scores, logistic for MOUD engagement and presence of risk factors). The model includes a random intercept and random linear slope to account for person-level clustering and estimate variable time trends across participants. To allow for curvilinear change over time, time will be entered as a nominal variable by including dummy codes for the 3- and 6-month time points. The explanatory variable of interest will be group randomization status (e.g., intervention versus control). Main effects and interaction terms capture the difference between intervention and control group at each wave. Covariates will be included if they are theoretically related to both the dependent variable and the probability of having missing data. An alpha level of 0.05 and two-tailed tests will be used to determine statistical significance. Results for continuous variables will be presented as adjusted differences between groups with confidence intervals. Results for dichotomous variables will be presented as

adjusted odds ratios with confidence intervals. **Missing Data -** We will examine patterns of missing data to determine the degree to which the missing at random assumption (the degree to which missingness is related to variables included in the model) is plausible. With high missing rates, we may use missing data methods to account for missing not at random mechanisms. If warranted, multiple imputation or similar methods will be used to account for missing data on completed or partially completed baseline and follow-up surveys (e.g., skipped items).

Pre-Post Screening Analysis of Pre-Post Trial – Because the clinics will not have the capacity to analyze data at the level of the individual patient, each clinic will calculate the proportion of patients in the pre-screening sample with a new OUD diagnosis and the proportion of patients in the post-screening sample with a new OUD diagnosis. Each clinic will report these two proportions to the investigative team, and we will compile a dataset with 24 observations (2 observations from each of the 12 clinics in each trial) and two variables: 1) proportion with a new OUD diagnosis and 2) a dummy variable indicating pre- or post-screening time period). For each clinic we will compute the change in proportion from pre- to post-screening. Because the pre-screening proportions are expected to be low (~1%)[75], the change measures will likely be skewed due to a floor effect. Also, the homogeneity of variance assumption could be compromised if the numbers of patients in the denominators vary considerably. For these reasons, we plan to use the non-parametric sign test to evaluate the statistical evidence indicating whether the proportions have changed. The numbers and proportion of the 12 clinics in each trial that see an increase in proportion of documented OUDs will be tabulated. The overall increase in proportion will be estimated with the mean of the clinic changes, weighted by the inverse variances, assuming binomial distributions for the pre- and post-screening numbers of documented OUDs. A bootstrap empirical 95% confidence interval will be computed for the estimate of overall proportion increase.

9.4.4 BASELINE DESCRIPTIVE STATISTICS

Categorical data collected at baseline will be presented as percentages. Continuous data will be presented as means with standard deviations. Because we are using cluster randomization with a relatively small number of randomization units, t-tests and chi-squares will be used to test for group differences at baseline.

9.4.5 SUB-GROUP ANALYSES

Because there is evidence that CoCM is more effective for women and minorities, we will conduct a moderation analysis (interaction term between sub-group and intervention group) for our primary outcomes.

9.4.6 EXPLORATORY ANALYSES

Exploratory Implementation Outcomes for Pre-Post Sustainability Evaluation– Participating intervention clinics continuing into the sustainability phase will continue to use the CMTS registry, and we will rely on data from CMTS and provider and clinic level surveys to monitor the implementation success metrics (adoption, reach, effectiveness and intervention fidelity). *Reach* will be measured by the number of patients receiving MOUD and evidence-based treatments for MHS. *Adoption* will be measured by the number of primary care providers prescribing MOUD and psychotropics for MHS.

Effectiveness will be measured using measurement-based care data. Implementation *fidelity* will be measured using the CoCM principles fidelity rubric modified for CHAMP. These six implementation outcomes will be measured at the end of the effectiveness trial and again after six months.

Quantitative Analysis for Pre-Post Sustainability Evaluation - These implementation outcomes measured at end of effectiveness trial will be compared to the implementation outcomes measured at the end of the sustainment period (after six months). The small sample size (n=6 clinics from 4 healthcare systems) will not give us sufficient power to detect anything but large effects. However, we will be able to see trends over time and to compare these distal implementation outcomes to those measures obtained during the effectiveness trial.

Qualitative Data Collection and Analysis for Pre-Post Sustainability Evaluation - We will supplement the quantitative data with qualitative data collected from clinic staff. Purposive sampling will be used to identify stakeholders from each of the 6 clinics. All interviews will be conducted via interactive video (Zoom). **Recruitment/Consent -** Eligible stakeholders will be identified by the study lead at each clinic. After a stakeholder has been identified, research staff will recruit them by email and or phone. Stakeholders will be considered study participants. We will mail or email stakeholders the "CHAMP Summative Evaluation Information Sheet". We will obtain an audio-recorded verbal agreement to participate in the qualitative interviews rather than written informed consent because the signed consent form would be the only identifying information collected (thereby increasing the risk of loss of confidentiality). In addition, participation in the qualitative interviews is considered to be no more than minimal risk. **Interview Guide:** The interview guide is organized by type of implementation outcome (sustainment mechanisms of action, proximal, distal), and three types of determinants that can be a barrier or facilitator of implementation success: 1) outer setting, 2) inner setting, and 3) fit between the clinical intervention and the outer and inner settings. A blend of grand-tour and specific probe questions will be used. **Analysis -** Using a typology of mixed method approaches, we will use the qualitative data to provide convergence with the quantitative data. This will include: 1) triangulation across data streams to corroborate findings (focusing on distal outcomes), 2) complementarity to gain additional depth of understanding and focus on process and context (across all outcomes), and 3) development of a conceptual model used to generate hypotheses. Two qualitative data analytic approaches will be used. A directed content analytic approach will be used to assess the distal implementation outcomes. This approach blends deductive and inductive analysis and will be used to provide depth and context to site level performance data on reach, adoption, and fidelity. A more grounded thematic analysis approach will be used to examine the potential impacts of the sustainment strategies on the proposed mechanisms of action and proximal outcomes. This approach will be largely inductive and focused on developing an initial model of mechanisms of action.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention. The consent form is included with this protocol.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

After a patient has been determined to be eligible (see eligibility workflow in section 5), clinic staff will recruit and consent the patient. Clinics will maintain electronic or hardcopies of the original consent form. Patients will be given an electronic or hardcopy of the signed consent form. Staff will not sign the consent form as a witness to the signature. Clinics may consent patients in one of two ways: in-person consenting or virtual e-consenting.

1. In-person consenting: clinic staff will provide information about the study to the patient in person using a REDCap e-consent form or a hardcopy of the informed consent form. Clinic staff will facilitate patient comprehension by providing opportunity for patient to consider the information and ask questions. Clinic staff will document consent using a REDCap e-consent form on a tablet or a hardcopy of the informed consent form. The signed REDCap e-consent form will automatically save a PDF of the electronic consent form that is immediately accessible to the UW study team to verify that the patient has enrolled in the study. A scanned PDF of the signed hardcopy consent form will be sent to UW to verify that the patient has enrolled in the study and to ensure that signatures are valid and dates are present.
2. Virtual e-consenting: clinic staff will provide information about the study to the patient virtually by tele-video or audio-only telephone. Clinic staff will facilitate patient comprehension by providing opportunity for patients to consider the information and ask questions. Clinic staff will document consent using a REDCap e-consent form or a hardcopy of the informed consent form. The REDCap e-consent form will be emailed to the patient to sign on their phone or computer. The hardcopy informed consent form can be mailed to the patient and returned if email is not available to the patient. The signed REDCap e-consent form will automatically save a PDF of the electronic consent form that is immediately accessible to the UW study team to verify that the patient has enrolled in the study. A scanned PDF of the signed hardcopy consent form will be sent to UW to verify that the patient has enrolled in the study and to ensure that signatures are valid and dates are present.

The modified[76] informed consent process will disclose the general purpose of the study, the evaluation data collection research activities, the risks of participating in the data collection activities, the protection against those risks, and the alternatives to participating, but patients will not be told which study arm their clinic has been randomized to.[77] We chose to not disclose this information to support the internal and external validity of the Effectiveness trial.

Consent forms will be available both in English and in Spanish.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the study participants, funding agency, and

regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor/funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party.

The data files with eligibility criteria, survey response and information extracted from CMTS will not contain any identifying information about study participants, but will contain a unique study ID. We will maintain a separate file that contains the study ID and participant's identifying information. This separate file containing participant's identifying information will only be available to the study team, and organizations that make sure studies like this are done safely. Specifically, the Institutional Review Board, the National Institutes of Health, and the federal Office for Human Research Protections will be able to inspect and copy confidential study-related records which identify study participants' by name. This is to make sure the research team is conducting the Effectiveness trial safely and legally.

Certificate of Confidentiality – This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, or documents that may identify study participants in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless a study participant has consented for this use. Information, or documents protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure or if a study participant has consented to the disclosure, or if it is used for other scientific research, as allowed by federal regulations protecting research subjects. The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the agency which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of, for instance, child abuse or neglect, harm to self or others, and communicable diseases. If we learn that study participants intend to harm others, we will report that to the authorities. Also, if a study participant reports that they intend to harm themselves, we will connect them with professionals trained in suicide prevention and notify their primary care team.

10.1.4 KEY ROLES AND STUDY GOVERNANCE

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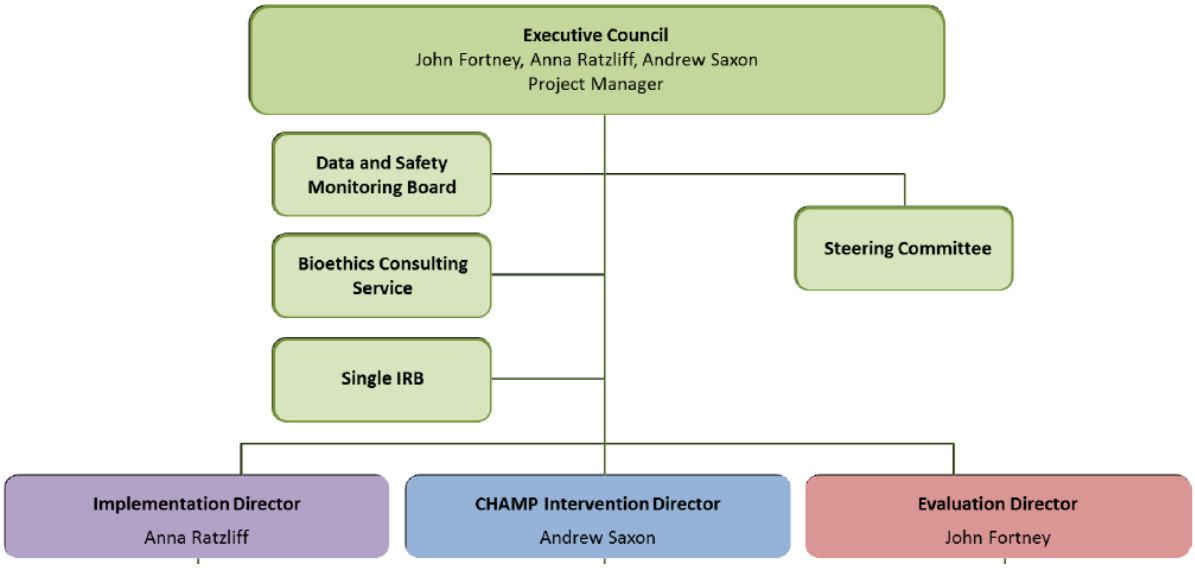

The organizational chart shows the structure that will be used to manage the trial and insure timely accomplishment of study aims. Each key area of the trial (Intervention, Implementation, Evaluation) will be led by one of the MPIs. Content areas within each of these will be led by one or more co-investigators who have relevant expertise. The weekly meetings associated with each of these key areas will produce agendas and minutes posted on a shared password-protected project management website for all investigators and members of the Steering Committee to review and in case of absence. Coordination of communication among the committees and teams will be the responsibility of the project manager who will establish a password-protected project management website where study materials, schedules and meeting minutes and other study documents can be shared. The program manager will support the easy flow of information among the multiple layers of trial staff, faculty and clinical organizations, including the external IRB, and Institute for Translational Health Sciences (ITHS), which will conduct data collection, provide bioethics consultation, and data safety monitoring.

Executive Committee – This committee consist of the three MPIs and the project manager. It will meet weekly to review ongoing progress of the study and to resolve operational issues as they arise. This group will regularly review data collection reports produced by the Institute for Translational Health Sciences (ITHS), data management reports produced by the Data Manager and Statistician, training and

implementation updates and intervention updates. These reports will assist the Executive Committee with insuring the study is accomplishing milestones on time. This committee will regularly review budget and expenditures to ensure that the study spends funds at the appropriate and proposed rate and has the resources to complete the tasks as outlined in the grant. This committee will have responsibility for publications arising from the trial, including CHAMP scientific conference presentations, prioritization of manuscripts that arise from CHAMP. According to the publications policy approved by the Steering Committee, this team will be proactive about inviting investigators to author and co-author papers and presentations. This group will produce a semi-annual report of activities and progress toward study goals for the Steering Committee.

Steering Committee – This is the governing body of the trial. The Steering Committee will be comprised of the MPIs, key personnel, NIH Project Scientist(s), clinicians and/or health system leadership for each of the participating clinics, an ITHS bioethics expert, and five (5) additional members that reflect the diversity of mental health and addiction stakeholders, such as patients and health policy makers will meet semi-annually to plan research activities, review study progress, and establish priorities, policies, and procedures related to the CHAMP trial. Each member of the committee will have one vote in decisions made by the Steering Committee with respect to study policies and procedures. Adoption of policies and procedures will require a majority vote. These policies and procedures will include publication policies. The chair of this committee will rotate among the MPIs on a yearly basis such that the chair of the Executive Committee and Steering Committee are not the same person in a given year. NIH Program Officials may attend Steering Committee meetings as non-voting members.

CHAMP Intervention Team – This group, led by MPI Saxon, will meet weekly during the implementation phase of the trial. The purpose of this team is to monitor the CHAMP clinical intervention at participating clinics, insuring the intervention protocol is aligned with current evidence-based treatment guidelines for co-occurring OUD and mental health conditions. This group will meet with the ITHS bioethics consultant in Year 1 to refine the Intervention Treatment manual and will meet with the bioethicist, as needed, on an ad hoc basis. This team includes MOUD experts (led by Saxon and Duncan), Collaborative Care experts (Unützer and Ratzliff), and clinical content experts representing primary care (Merrill, Duncan), child psychiatry and substance use (Hsiao), psychosocial supports (Simpson), and perinatal psychiatry (Bhat). This group will produce a semi-annual report of activities and progress toward study goals for the Steering Committee.

Implementation Team – This group, led by MPI Ratzliff, will meet weekly during the implementation and sustainability phases of the trial. The purpose of this team is to monitor training, CoCM and CHAMP external facilitation during the Effectiveness trial, internal and external facilitation during the sustainability phase, and formative evaluation activities during both the Effectiveness trial and sustainability phase. This team includes the two Clinical Implementation Support Leads from the AIMS Center conducting practice facilitation with participating clinics (Shields, Barker) and the formative evaluation experts (Williams, Lewis). This group will produce a semi-annual report of activities and progress toward study goals for the Steering Committee.

Evaluation Team - This group, led by MPI Fortney, will meet every other week during the data collection and analysis phases of the trial. It will have responsibility for designing, monitoring, and supporting all evaluation activities for CHAMP, including reviewing data collected, data quality, and similar throughout the trial. Membership include the quantitative leads (Heagerty, Bowen) and the summative evaluation leads (Curran, , and Drummond) as well as the data manager and other evaluation staff as needed.

10.1.5 SAFETY OVERSIGHT

Data and Safety Monitoring Plan

General Procedures – The Multiple PIs will be primarily responsible for day to day data safety and monitoring. The PIs will ensure that informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan. Random audits for data safety may be performed by the IRB.

DSMB -- Monitoring for the study will be provided by a NIMH appointed DSMB, including data and safety monitoring and review three times a year. The DSMB will meet to review enrollment data, adverse events, data quality and integrity of protocol implementation. The DSMB will provide a written report to the study team with recommendations for study modification, and has decisional authority with respect to study initiation, and study continuation/discontinuation. The UW study team will be responsible for forwarding DSMB decisions to the IRB.

10.1.6 STUDY MONITORING

Research staff at the University of Washington will meet with sites biweekly to review recruitment procedures including eligibly assessment and consenting, as well as facilitate to adverse event reporting. Adverse Events reported from the sites will be promptly reviewed by a multiple PI to determine study relatedness. Adverse Events will be logged by sites into RedCap, which will automatically alert the multiple PIs via email until they are resolved. The multiple PIs and research coordinators will review eligibility and adverse event reports during weekly meetings.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Federal Wide Assurances (FWA) – Federal Wide Assurance documents issued from OHRP (including expiration dates) will be kept on file.

IRB Records – All single IRB and local IRB records and correspondence will be maintained in electronic format.

Training in Human Subjects Training – The Project Coordinator will ensure that all study personnel have documentation of completing all required human subjects protection training. In addition, the Project Coordinator will ensure documentation that those obtaining informed consent have completed the consent training specific to this study.

Eligibility Tracking – All patients screening positive for OUD (potentially eligible) will be entered into the Eligibility RedCap project where exclusion criteria and refusals will be documented. The Eligibility RedCap project will also be the repository of all scanned signed consent forms.

Informed consent – A UW research coordinator will review the documentation of the consenting process, as well as a percentage of eligible patients completing the consent process. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the on-site study team to ensure proper consenting procedures are followed, and that all consented patients were eligible.

Source documents and the electronic data – All data will be captured electronically (see **Section 10.1.9, Data Handling and Record Keeping**).

Intervention Fidelity – Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.

Data Integrity – The data analyst will review electronically collected study data for any problems (e.g., missing, out of range data).

Adverse Event Report – All adverse events will be entered in the AE/SAE log of the RedCap Study project. All site-specific SAE reports will be on file, including documentation of reporting to the NIMH and the DSMB.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions. Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities. See **Section 8.4.1, Definition of Unanticipated Problems** and **Section 8.4.2, Unanticipated Problems Reporting**.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Sources of Materials

Sources of research materials include the following:

EHR Data (Non-Indefinable) – Pre- and Post-Screening data (numerator [OUD diagnosis] and denominator [unique patients] will be calculated by each healthcare organization using EHR queries and recorded in an excel spreadsheet. The excel spreadsheet (which contains no patient health or identifying information), will be emailed to the study team at the University of Washington. Data will be reviewed by University of Washington statisticians and data managers and discussed with the on-site study team. This data will be used for the Secondary Objective (Pre-Post Trial).

Eligibility Data and Consent Forms – The eligibility information for all patients screening positive for OUD will be entered directly into RedCap by the on-site study team. Signed consents forms, will be scanned and attached to the RedCap study portal. Eligibility data will be reviewed by a University of Washington PI and the study coordinators, and discussed with the on-site study teams. This data will be used for the Primary Objective (Effectiveness trial).

Personal Identifying Information – Identifying information (e.g., name, address, telephone number, email, and contacts) about patients consenting to be in the Effectiveness trial will be stored in a single file along with a unique study identifier. This data will be used for the Primary Objective (Effectiveness trial).

Surveys - The patient web/telephone survey will be administered at baseline, 3- and 6-month follow-ups. All survey responses are stored directly into a RedCap database. This data will be used for the Primary Objective (Effectiveness trial).

Adverse Events – Information about all Adverse Events, Serious Adverse Events, Unanticipated Problems, and Potential Loss of Confidentiality will be entered directly into RedCap by the on-site study team and reviewed/edited by the research team. This data will be used for the Primary Objective (Effectiveness trial), as well as for regulatory purposes.

CMTS (Care Management Tracking System) registry – The CMTS, a registry that facilitates delivery of CoCM, contains clinic-level process of care and patient-level clinical outcome data that shows how patients receive care. The CMTS registry already contains the mental health and substance use diagnoses, as well as results from the OUD, depression, anxiety and PTSD measure-based care scales that will be used to monitor treatment response for this trial. CMTS also records care manager encounters, delivery of behavioral activation, and psychiatric case reviews.

Data Security – Standard safeguards to protect research data will be followed. All study participants will be assigned a unique identification number. All data will be collected with only this unique identifier attached and no identifying information. All de-identified and identifiable information about participants will be maintained in separate password-protected folders on encrypted secure servers hosted behind the University of Washington's network firewall. The file with Personal Identifying Information will be stored separately from deidentified information. These eligibility, survey, adverse events, and CMTS data streams will eventually be merged using the unique participant identifier to create an analytical dataset. A data dictionary will created for this analytical dataset. Only certain research staff will have access to these databases. All study staff will undergo human subjects training. Study data will only be kept as long as required by law before it is destroyed in a manner that will protect confidentiality. We expect that these measures will be effective in protecting against loss of confidentiality.

10.1.8.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 3 years after the study end date.

10.1.9 PUBLICATION AND DATA SHARING POLICY

Publications – The Executive Committee will have responsibility for publications arising from the trial, including CHAMP scientific conference presentations, prioritization of manuscripts that arise from CHAMP. According to the publications policy approved by the Steering Committee, this team will be proactive about inviting investigators to author and co-author papers and presentations. This study will be conducted in accordance with the National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

Data Sharing – This study will be conducted in accordance with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 1 year after the completion of the primary endpoint by contacting the AIMS Center at the University of Washington. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

10.1.10 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The Executive Council will establish policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest. Importantly, this study is not testing a drug, device or treatment manual, and thus the potential for a financial conflict of interest is minimal. The University of Washington requires all investigators to sign annual conflict of interest forms, and all investigators signed a conflict of interest form for the CHAMP study specifically.

10.2 ADDITIONAL CONSIDERATIONS

Oversight for the CHAMP study is being provided by the Advarra Single IRB. Due to the COVID pandemic, we may need to make protocol modifications to the approved protocol, including requesting to obtain e-consents in the event that COVID-19 prevents in-person healthcare encounters. We will be considering these as we get closer to fielding the trial and have a better sense of the impact of the COVID pandemic on the functioning of our sites.

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
CFR	Code of Federal Regulations
COC	Certificate of Confidentiality
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Council on Harmonisation
IRB	Institutional Review Board
ISM	Independent Safety Monitor
NCT	National Clinical Trial
NIH	National Institutes of Health
NIDA	National Institute on Drug Abuse
NIMH	National Institute of Mental Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
UP	Unanticipated Problem

Study Specific Acronyms Definitions

AIMS – University of Washington's Advancing Integrated Mental Health Solutions
ASSIST – Alcohol, Smoking and Substance Involvement Screening Test screener
AUDIT-C – Alcohol use/consequence rating scale
BA – Behavioral Activation psychotherapy
BAM-R– Drug use/consequence rating scale - revised
CDC – Centers for Disease Control and Prevention
CESATE – Center of Excellence in Substance Abuse Treatment and Education
CHAMP – CoCM for MHS and OUD
CMTS – Care Management Tracking System
CoCM – Collaborative Care Management
DAP – Dynamic Adaption Process framework
DATA 2000 – Drug Addiction Treatment Act of 2000
DSM-5 – Diagnostic and Statistical Manual 5
EHR – Electronic Health Record
FDA – Food and Drug Administration
GAD-7 – Generalized Anxiety Disorder scale
ICR – Importance-Confidence-Readiness
MCS – Mental Health Composite Summary
MOUD – Medication for Opioid Use Disorder
MHD – Mental Health Disorder
MHS – Mental Health Symptoms
MPI – Multiple Principal Investigator
OUD – Opioid Use Disorder
PC-PTSD-5 – Primary Care PTSD Screener for DSM5
PEG -- Pain, Enjoyment of Life and General Activity scale
PCL-5 – PTSD Checklist for DSM-5
PCORI – Patient Centered Outcomes Research Institute
PHQ-9 – Depression scale
PMID – Prescription Drug Monitoring Program
PROMIS -- Patient-Reported Outcomes Measurement Information System
PTSD – Post-traumatic stress disorder
RCT – Randomized Controlled Trial
SAMHSA – **Substance** Abuse and Mental Health Services Administration
SCL-20 – Symptom Checklist 20
SOS – Short Opioid Screen
SSRI – Selective serotonin reuptake inhibitor
SUD – Substance Use Disorder

Protocol Amendment History

*The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A **Summary of Changes** table for the current amendment is located in the **Protocol Title Page**.*

Version	Date	Description of Change	Brief Rationale
2	3.27.2020	1. Changed the name of the intervention group from "CHAMP" to "intervention group" and the control group from "CoCM for MHD" to "control group". 2. Change the trial design from two parallel trials to one trial with two cohorts. 3. Excluded children under the age of 18. 4. Dropped the requirement to recruit clinics from areas with high levels of opioid overdoses. 5. Revised the specifications of the numerator and denominator groups for Aim 1. 6. Added inclusion criteria that patients could be referred into the study. 7. Added inclusion criteria that study participants must have at least two symptoms of opioid use disorder as assess by a clinician use the DSM-5 checklist. 8. Added that we will be collecting information from the state Prescription Drug Monitoring Program. 9. Added information about the anticipated risks. 10. Revised the consent form to reflect these modifications. 11. Revised the HIPPA authorization form.	1.This was done to increase clarity and to not conflate the study name with the name of the intervention group. 2. This was done to improve the balance of the intervention and control groups. 3. The clinics prefer that we know enroll children in the trial. 4. We needed to relax this requirement in order to recruit enough clinics. 5.These changes were made to accommodate limitations of EHR queries and to increase clarity. 6.This change was made at the request of the participating clinics. 7. This was added to ensure that referred patients meet criteria for opioid use disorder. 8.This information about dispensing was added to triangulate information about prescriptions and patient self-reported use of prescribed opioids. 9.This was added so that we could classify adverse events as anticipated or unanticipated. 10. These revisions were made to that the consent form was consistent with changes to the protocol. 11.The HIPPA authorization form was revised to be compliant with Washington state law.

Version	Date	Description of Change	Brief Rationale
3	8.24.2020	1. Dropping the word "pragmatic" from the description of the trial. 2. Revised Eligibility Criteria a. No longer excluding new clinic patients from the trial in the first six months b. Spanish Speaking Patients are now eligible. c. We will exclude patients who are receiving or seeking treatment in specialty mental healthcare setting. d. Replacing the PCL-5 with the PC-PTSD-5 screener to determine PTSD inclusion criterion. 3. Adding that the PCL-5 will be used for the Measurement Based Care component of the interventions 4. Adding more details about the Formative Evaluation and requesting a Waiver of Written Informed Consent for Formative Evaluation research activities. 5. Adding e-consenting and dropping the requirement that staff sign as witnesses to consenting. 6. Redefining how one of the outcomes (MAT Persistence) will be measured. 7. Adding that chart review will be used to identify opioid prescriptions. 8. Revisions to the safety planning protocol for patient reporting suicide intent on the survey. 9. Replacing the PDS-5 with the PCL-5 as the way to measure PTSD severity in the survey. 10. Changing in the ICF that we will collect data about their care from "three months before today until seven months from today" instead of "today until thirteen months from today."	1. We determined that this term was in inaccurate description of the trial since we would be controlling fidelity of the intervention delivery. We also made some non-significant wording changes throughout and corrected typos. 2a. We determine that clinics could drop new patients from the EHR queries and thus recruitment of new patients into the trial would no long bias the results of Aim 1. 2b. Participating clinics wanted us to include Spanish speaking patients. 2c. We added this exclusion criteria to include those receiving non-pharmacologic treatments in specialty settings. This is consistent with our similar exclusion criteria of receiving prescriptions for psychotropic medications from a mental health specialist. 2d. Replacing the PCL-5 with the PC-PTSD-5 screener to determine PTSD inclusion criterion. 3.We inadvertently neglected to include the PCL-5 previously. 4.The Formative Evaluation activities were only vaguely described in the previous protocol. All Formative Evaluation activities are considered minimal risk and we a request a waiver of documentation of written informed consent. 5.Because of Covide-19 we need to be able to obtain consent remotely using e-consenting procedures. Staff obtaining informed consent cannot witness e-signatures, so we are removing that element of the ICF. 6. Because we have determined that we may not be able to obtain data from the state Prescription Drug Monitoring Programs, we changed how we would measure MAT persistence. We are now relying on self-report.

			7.Because we have determined that we may not be able to obtain data from the state Prescription Drug Monitoring Programs, we are now using chart review to identify prescriptions for opioids written in the primary care clinic. 8.We broke up the safety plan question into separate questions in an attempt to encourage survey respondents to agree to the best safety plan (the questions are now ordered by our ranking of safety). 9.Tthe PDS-5 had inferior face-validity than the PCL-5 10.The 13 months from today was a typo. Also, we wanted to be able to collect pre-baseline opioid prescription information from the chart review and the Prescription Drug Monitoring Program.
4	3.17.21	1. Clarifying the language for patient eligibility exclusion criteria to clarify that we will: a. allow patients receiving a current prescription if the prescriber is an addiction specialist and is a primary care provider in the clinic or health system). b. who are or have been enrolled in CoCM for co-occurring disorders for more than 14 days because their baseline survey responses will not be documented prior to receiving the intervention. 2. Adding information to Virtual e-consenting process to clarify that the and the patient can receive the e-consent form via text and will receive an signed PDF of the e-consent form via email or text.	1. to clarify the exclusion ctieria for the clinics and to make study criteria more inclusive. 2. Required by the IRB to clarify the e-consent process in the ICF and the protocol.
5	6.25.21	Submitted the IRB protocol changes in review 1. Screen positive on the NIDA-ASSIST OUD or the Short Opioid Screen (SOS) for OUD items OR referred to the trial by one of the clinic's providers. 2. Added to inclusion criteria "meet clinical criteria for ≥2 symptoms of OUD on the DSM-5 checklist (administered by a clinician)" to include "and/or OUD diagnosis recorded in the electronic medical record and a patient encounter in the past 6	1. Many of the clinics reported that patients did not understand the NIDA-Modified Assist for OUD questions and staff found it difficult to score. Therefore we created a shorter, simpler, two-item screener for OUD an are giving the clinics the option to use the two-item screener for OUD instead of the NIDA-Modified Assist for OUD. We have named this screen the Short Opioid Screen (SOS) 2. We were finding that many patients screening positive for OUD were being diagnosed with OUD but the number of

		months or OUD diagnosis on problem list PCP reviewed in the past 6 months." 3. Added language to clarify the patient baseline survey interviews will be completed within 14 days of the consent signed date and follow-up interviews will be completed within 42 days of the target date.	DSM-5 checklist symptoms were not being recorded in the Electronic Health Record. As a result, we have been unable to enroll many patients who met inclusion criteria due to the lack of documentation of the number of DSM-5 checklist symptoms. 3. This was not previously specified, but we wanted to update the protocol with these details. `
6	3.15.22	1. Description of Sites/Facilities Enrolling Participants: Twenty-four clinics from 8 healthcare systems are participating. Updated 1.1 SYNOPSIS, Page 2	Modified text to address changes since the last review.
		2.We will encourage chain recruitment from existing CHAMP patients. We will offer referring patients $50 for each patient that meets inclusion criteria for CHAMP. We will send eligible patients to the clinic that is closest in proximity to their home. Updated 5.4 STRATEGIES FOR RECRUITMENT AND RETENTION, Page 14.	Due to continued slow recruitment, we have introduced payment to existing patients to refer other patients to the CHAMP study.
		3.UW staff will be trained to obtain written informed consent to the patient virtually by tele-video or audio-only telephone Updated 10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION, Page 32.	To address clinic expressed anxiety and lack of time to consent, we have added the option for a UW staff person to virtually consent an eligible patient for CHAMP.
		4.We have updated the power analysis to include a lower bound scenario. Updated 9.2 9.2 SAMPLE SIZE DETERMINATION, Page 28	To address reduced enrollment.
7	7.15.22	1. Updated Study Duration (to 39 months total) to reflect the extension of enrollment to 33 months total Updated 1.1 SYNOPSIS, Page 2	Modified text to address changes since the last review due to the extension of recruitment timeline. Total treatment period will be 39 months.
		2.Updated Study Design to reflect the extension of enrollment. Updated 1.2 SCHEMA, Page 3	Modified text to address changes since the last review due to the extension of recruitment timeline.
		3.Updated the enrollment timeline from 24 months to a 33-month period. Updated 5.4 Page 15, STRATEGIES FOR RECRUITMENT AND RETENTION	Modified text to address changes since the last review due to the extended timeline.
		4. Updated to include non-lethal overdose categories per DSMB requestion 06. Non-lethal overdose (that resulted in hospitalization or ED visit) 07. Non-lethal overdose (that did not result in hospitalization or ED visit) Updated 8.2.2, Page 23 SERIOUS ADVERSE EVENTS	To address the request of the DSMB to include these categories.
Version	**Date**	**Description of Change**	**Brief Rationale**

8	3.15.2023	1.1 Synopsis	Study Population – increased the # of Clinics and states participating in CHAMP.
		1.3 Schedule of Activities 8.1 Endpoint and Other Non-Safety Assessments 9.4.3 Analysis of the Secondary Endpoint(s)	The label for the anxiety measure in the survey was Neuro_QOL, but was mislabeled as PROMIS.
9	6.26.23	Study Population – increased the # of Clinics and states participating in CHAMP.	We updated the number of clinics and states from 24 to 38 clinics and from 8 to 10 states. Age, gender and race/ethnicity will be representative of the demographics and epidemiology of the clinics.
		Description of Sites/Facilities Enrolling Participants – increased the # of Clinics and states participating in CHAMP.	Sites include a range of primary care settings in the United States. 38 clinics from 10 healthcare systems are participating.
10	10.16.23	Study Population – increased the # of Clinics and states participating in CHAMP.	We updated the number of clinics and states from 38 to 42 clinics and from 10 to 12 states. Age, gender and race/ethnicity will be representative of the demographics and epidemiology of the clinics.
		Description of Sites/Facilities Enrolling Participants – increased the # of Clinics and states participating in CHAMP.	Sites include a range of primary care settings in the United States. 42 clinics from 15 healthcare systems are participating.
11	9.16.24	Aim 3 – Change the sustainability implementation trial to a pre-post evaluation.	Because we extended the recruitment period for the effectiveness trial, there was insufficient time to conduct the implementation trial.

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