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Official Title: Study Protocol for ‘Mindful Body Awareness with Medication Treatment for Opioid Use Disorder’

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MABT for OUD Protocol

Version 4.0
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PREFACE

The objective of this study is to test the effectiveness of an innovative body-oriented therapy found to reduce substance use and improve related health outcomes as an adjunct to opioid use disorder (OUD) treatment. The long-term study goal is to improve OUD treatment outcomes. Body-oriented therapy combines manual and mind-body elements and is focused on improving sensory and emotional awareness. The approach, Mindful Awareness in Body-oriented Therapy (MABT), involves body awareness (e.g. interoception) training to provide somatically-based tools for self-care to facilitate emotion regulation. Research suggests that only half of persons who are treated with buprenorphine are retained in maintenance treatment beyond 6 months, and when not taking medications patients frequently relapse to illicit opiate use. Chronic pain has been identified as a major factor that may lead to treatment failure. In a sample of patients on MAT, we demonstrated that patients with chronic pain were more likely to report cravings for opiates. Chronic pain is unfortunately common among persons with OUD: studies suggest that the majority of patients on methadone and buprenorphine suffer from chronic pain.

Relapse prevention is critical to positive outcomes in opioid abuse treatment and studies indicate that stress, negative affect and poor emotional regulation are associated with vulnerability to relapse. MABT has the potential to address relapse to substance use, chronic pain and its associated stress, and thus improve treatment outcomes among patients being treated for OUD with buprenorphine.

There is a compelling need for adjunctive therapies to maximize treatment outcomes for patients who are receiving buprenorphine for OUD treatment. This research study responds to the need to test new OUD treatments, particularly innovative approaches that target interoception and emotion regulation to enhance treatment outcomes. This study will be implemented through the Opioid Strategic Targeted Response (STR) program. Consistent with RFA-AT-18-001, *Behavioral Interventions for Prevention of Opioid Use Disorder or Adjunct to Medication Assisted Treatment-SAMSHA Opioid STR Grants*, and RFA-AT-19-007, *HEAL Initiative Limited Competition: Behavioral Research to Improve MAT: Ancillary Studies to Enhance Behavioral or Social Interventions to Improve Adherence to Medication Assisted Treatment for Opioid Use Disorders (R01 Clinical Trial Optional)*, the proposed project expands the study of MABT to MAT of OUD, with an emphasis on comorbid pain.

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Mindful Body Awareness Training as an Adjunct to Medication Assisted Treatment for Opioid Use Disorder

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Tool Revision History

Version Number: 1.0
Version Date: December 6, 2018
Informed Consent Version: 1.0 (approved 12/21/2018)

Version Number: 2.0
Version Date: January 22, 2019
Informed Consent Version: 1.0 (approved 12/21/2018)
Informed Consent Version: 1.1 (approved 3/20/2019)
Summary of Revisions Made:

- Changed performance site from Evergreen Treatment Services to Country Doctor Community Health Centers
- Revised Objective 1 to include a focus on emotional well-being.
- Two measures focused on emotional well-being added.
- Supervision of MABT therapists to be done by Ms.Wiechman (not by Dr. Price).
- Clarifications made to document, in response to Dr. Boineau January 18 review.

Version Number: 3.0
Version Date: November 7, 2019
Informed Consent Version: 1.1 (approved 3/20/2019)
Informed Consent Version: 1.2 (approved 8/2/2019)
Informed Consent Version: 1.3 (approved 10/4/2019)
Informed Consent Version: 2.0 (approved 10/16/2019)
Summary of Revisions Made:

- Adapted Clinical Protocol to include extension of activities of R01 proposal:
    - Extend follow-up to five assessments over one year
    - Add North Olympic Healthcare Network as recruitment site
    - Increase total sample size to 330
    - Offer a stepped-care approach to MABT participants at six months
- Added personnel information to study contacts
- Require HIPAA permission to participate in research study
- Randomization occurs in a Microsoft BASIC program and the algorithm is described
- Added source documentation by Clinical Staff at time of referral for 2 eligibility criteria: OUD and 4 weeks of buprenorphine Rx
- Specified use of an adapted 7-item Mini-Mental Status Exam in case of concern for comprehension of consent or cognitive difficulties (ie head injury)
- Expanded to licensure required for MABT therapists to include either LMT or MSW/LMHC.
- Clarified allowable study visit windows, and optimization of data collection during ideal collection windows
- Non-substantive changes to update described procedures such as when screening ID number is assigned, collecting preferred participant contact methods, etc. based on further communications with clinical sites and training/practice experience with new staff.

Version Number: 4.0
Version Date: October 20, 2021
Informed Consent Version: 1.1 (approved 3/20/2019)
Informed Consent Version: 1.2 (approved 8/2/2019)
Informed Consent Version: 1.3 (approved 10/4/2019)
Informed Consent Version: 2.0 (approved 10/16/2019)
Informed Consent Version: 3.0 (approved 9/02/2021)

Summary of Revisions Made:

- Added Clinical Site, Cascade Medical Advantage (CMA) in Bellingham, WA
    - This addition was taken to replace Country Doctor Clinic, where we stopped recruitment in May, 2021 due to insufficient support for enrollment by clinic staff.
- Added Clinical Site, Evergreen Treatment Services (ETS) in Seattle, WA
    - Since ETS is a methadone clinic (other clinical sites prescribe buprenorphine), we amended our eligibility criteria so that it aligned with the overall focus on stability in treatment (as at other sites) but addressed medication dispensing procedures for methadone.
    - Amended our informed consent so it could be used at all clinical sites, including ETS. This involved minor shifts in language (i.e. removing reference to buprenorphine and referring more broadly to medication for OUD treatment); see approval noted above on 9/2/21.
- Updated Study Roster
- Updated Study Clinical Sites
- Unsubstantial/minor revisions: updated language throughout to reflect focus on medication for OUD (vs. buprenorphine specifically).

TABLE OF CONTENTS

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PRÉCIS

Study Title

Mindful Body Awareness Training (MABT) as an Adjunct to Medication Assisted Treatment (MAT) for Opioid Use Disorder

Objectives

1. The primary objective is to evaluate the effectiveness of MABT + TAU compared to TAU only in reducing opioid use (OU) and other illicit substances (e.g. methamphetamines, etc.).

2. To examine the effectiveness of MABT + TAU to improve mental and physical health compared to TAU only.

3. To examine the effectiveness of MABT + TAU to positively affect substance use related outcomes of craving and treatment retention compared to TAU only.

4. To explore the effectiveness of additional MABT dose offered at 6 months to those with continued substance use (non-responders) compared to those with continued substance use at 6 months in TAU.

Design and Outcomes

A two-group (n = 165/165), randomized, repeated measures design will be employed in enrolled patients with opioid use (OU) disorder, who will be individually randomized within sites to receive MABT+TAU (experimental group), or TAU alone (control). MABT will be delivered as a stepped-care approach, involving an initial set of eight weekly sessions, with an additional six MABT sessions offered at six months to those with continued substance use in intervention arm. Assessments (surveys and toxicology screens) will be administered at baseline, post-intervention (3 months), and at 6 month, 9 month, and 12 month follow-up. Analyses at 12 months with a larger sample will examine long-term health outcomes of MABT +TAU compared to TAU only on: 1) opioid use and use of other non-opioid substances, 2) mental health (depression, anxiety, trauma), emotion regulation, and physical health

(symptoms, pain severity, pain interference); and 3) opioid craving and treatment retention. An exploratory aim will examine the effectiveness of additional MABT dosing for those in the MABT treatment arm with continued substance use (nonresponders) at six months compared to those with continued substance use (nonresponders) in the TAU arm.

Table 1. Measurement Schedule

Concept	Measure	Assessment Time-Point (from baseline)				
		Baseline	12 weeks	24 weeks	39 weeks	52 weeks
Baseline and Descriptive Information						
Demographic/Health History	Health History Form[1],(EHR)	X				
Trauma history	TLEQ[2]	X				
Economic Indicators	Employment, Health Utilization, Legal Status	X	X	X	X	X
Substance Use						
Substance use	TLFB Interview[3, 4] Opioid Craving [5] Treatment Retention (EHR)	X X X	X X X	X X X	X X X	X X X
Mental Health Distress, Emotional Well-being, Physical Health Distress and Pain						
Distress (Depression, Anxiety PTSD Symptoms)	PHQ-9[6, 7] GAD-7[8] PCL-5[9]	X X X	X X X	X X X	X X X	X X X
Emotional Regulation Difficulties	DERS-SF[10]	X	X	X	X	X
Mindfulness and Interoceptive Awareness Skills	FMQ [14] MAIA [15]	X X	X X	X X	X X	X X
Co-morbid Pain and Interference	BPI[18]	X	X	X	X	X
Physical Symptoms	MSC [19]	X	X	X	X	X
Intervention Satisfaction						
Treatment satisfaction and perceived skills*	MABT Follow-up Questionnaire		X			

*MABT Group only; EHR = Electronic Health Records.

Interventions and Duration

All study participants receive medication treatment for OUD with OUD treatment monitoring by a nurse care manager or medical provider (treatment as usual, or TAU) continually throughout the 12 month study. Those randomized to the intervention group will additionally receive Mindful Awareness in Body-oriented Therapy (MABT). The MABT protocol calls for eight sessions to be delivered over a 12 week period between baseline and the 12 week post-intervention assessment. At six months, those in the MABT+TAU treatment group with continued substance use will be offered an additional six sessions of MABT between the six month and 9 month assessments. Follow-up for all participants will total 12 months from the participant's first assessment point.

Sample Size and Population

330 male and female individuals who have been receiving MAT treatment for at least four

weeks will be recruited from three OUD clinical treatment sites. Each study arm will include 165 participants. Participants will be randomized within site, and stratified by sex and self-reported chronic pain; objectives and outcomes will not vary by strata.

We expect the clinical characteristics of study subjects to be similar to those enrolled in the SAMHSA Medication Assisted Treatment – Prescription Drug and Opioid Addiction (MAT-PDOA) project in Washington State. The patients at the two clinics have near equivalence in the numbers of men and women served, and age range (18 - 70 years old) with the majority (59%) under the age of 35. Most patients are white, low-income, have at most a high school education, and are on public insurance (Medicare or Medicaid), with substantial mental health and substance use co-morbidity. Approximately 25% are minorities.

1. STUDY OBJECTIVES

1.1 Primary Objective

Primary Objective and Hypotheses

The primary objective is to evaluate the effectiveness of MABT + TAU compared to TAU only in reducing opioid use (OU) and other illicit substances (e.g. methamphetamines, etc.).

Primary hypothesis: MABT+TAU will result in significantly fewer days of OU compared to TAU only from baseline to to 12 months.

Secondary hypothesis: MABT+TAU will result in significantly fewer days of non-opioid illicit drugs compared to TAU only from baseline to 12 months.

1.2 Secondary Objectives

1) To examine the effectiveness of MABT + TAU to improve mental and physical health compared to TAU only.

Hypothesis: MABT+TAU will result in significantly improved symptoms of mental health distress (depression, anxiety, trauma), emotion regulation, interoceptive awareness and mindfulness skills, and physical health distress and pain (symptoms, pain severity, pain interference) compared to TAU only from baseline to 12 months.

2) To examine the effectiveness of MABT + TAU to positively affect substance use related outcomes of craving and treatment retention compared to TAU only.

Hypothesis: MABT + TAU will result in significantly reduced craving for opioids, and significantly longer retention (days receiving medications), compared to TAU only from baseline to 12 months.

3) To explore the effectiveness of additional MABT dose offered at 6 months to those with continued substance use (nonresponders) compared to those with continued substance use at 6 months in TAU.

Hypothesis: Among participants in both groups who are using substances at 6 months, those in MABT group who receive additional MABT sessions (between 6-9 months) will

show improved substance use at 12 months compared to those in TAU.

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2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Federal and State Response to a National Crisis. Opioid use disorder is a public health epidemic of national significance, as demonstrated by federal efforts to target significant new public resources to address factors contributing to the continued rise in opioid related deaths.[20] The most effective intervention, which has been shown to reduce drug use, morbidity and mortality related to opioid use disorder, is Medication Assisted Treatment (MAT) with buprenorphine and methadone. Thus, a substantial portion of federal assistance is targeted at improving access to MAT, especially through Opioid State Targeted Response grants administered through states by SAMHSA. The Washington State Opioid State Targeted Response (WA-STR) grant is an $11.7 million per year project. WA state funded projects include prevention projects aimed at opioid prescribing practices and projects supporting treatment of OUD. The largest single project ($4 million per year) is the Hub and Spoke (H&S) project, which funds six OUD treatment networks in Washington State. This adaptation of the Vermont Hub and Spoke model funds six networks that each provides referral and/or treatment services through primary care clinics, behavioral health programs, and substance use disorder (SUD) treatment programs. Washington State was recently awarded over $21 million for its State Opioid Response (SOR) project, which is expected to continue currently funded WA-STR projects as well as funding new initiatives.

The research proposed here will be conducted through a WA-STR/SOR-funded H&S program taking place at Harborview Medical Center (HMC). The network expands ongoing work funded through the SAMHSA Medication Assisted Treatment – Prescription Drug and Opioid Addiction (MAT-PDOA) project in Washington State, which is piloting the expansion of MAT with buprenorphine through a primary care clinic and other Opioid Treatment Programs using the Massachusetts Nurse Care Manager (NCM) model. Other treatment models are also included in this study, depending on clinical site.

Need for Behavioral Interventions to Prevent Relapse and Address Mental Health and Chronic Pain Among Patients Treated with MAT for OUD. MAT has been shown to reduce illicit opiate use and improve health outcomes for patients with OUD;[21-29] however, not all patients will benefit, as treatment retention rates are unacceptably low. Data suggests that retention may be more of a problem for patients treated with buprenorphine compared to methadone: a secondary analysis of clinical trials found that retention at 24 weeks was 46% among buprenorphine treated patients compared to 74% among methadone treated patients ($p<0.01$).[30] Estimates of buprenorphine retention in real-world office-based settings show that approximately a half, or less, of patients who are initiated in treatment are still retained a year later.[31-34] Studies with Kaplan Meier data demonstrate a steep drop-off early in treatment with median retention ranges 3–9 months.[32, 35, 36] Clearly there is an

opportunity to intervene with patients initiating treatment with MAT to improve retention rates. The most common reason for patients to become disengaged and not be retained in care is relapse to substance use.[31] In addition, upon entering MAT, the majority (~52%) use multiple substances [37-40] and there is a high prevalence (34–57%) of co-morbid psychiatric disorders [38, 41-43] and social problems.[41, 44, 45] Post-traumatic stress disorder (PTSD) prevalence is 33–50% among patients in SUD treatment,[46] and elevated among those with opioid dependence.[47, 48]

Unfortunately, adjuncts to MAT such as counseling have failed to show improvement in outcomes over standard medical management alone.[49, 50] Poor treatment outcomes in this population are associated with the high prevalence of drug [38, 51-53] and alcohol use [39, 40] during treatment, psychopathology,[42, 54] and chronic pain.[45, 55, 56] The need for behavioral strategies as adjunctive treatment support for this population to address the high levels of psychological and physical distress and pain management is well-recognized.[37, 42, 56-59] However, to our knowledge, only one prior mind-body intervention, a pilot study of neurofeedback training, has been implemented as an adjunct to MAT for individuals with OUD;[60] results were promising, showing reduced opioid craving, depression, physical symptoms, and overall mental health distress. This study did not examine substance use outcomes other than craving, highlighting the need for more research like the proposed project to examine the potential benefit of adjunctive mind-body approaches to reduce substance use and prevent relapse among individuals in MAT for OUD.

Mind-body approaches have a high level of perceived effectiveness by OUD patients in MAT.[61] Notably, manual and mind-body approaches were the most sought-after treatments among MAT patients with chronic pain[62] and have been identified as viable adjunctive treatments needing research for individuals on MAT for OUD.[63] Two recent large RCT studies of mindfulness-based interventions for the treatment of chronic pain demonstrated reductions in pain in the experimental vs. control groups.[64, 65] Likewise, a pilot study of a mindfulness-based intervention for individuals using opioids for pain (but not in treatment for an OUD)[66] showed reductions in pain severity, pain interference, and opioid craving compared to an active control. Together these studies highlight the potential promise of a mindfulness-based approach such as MABT, the proposed intervention for this project, for this unique population.

Interoceptive Awareness and Substance Use. Interoception involves the processing of sensory input from inside the body[67] and interoceptive awareness involves the development of sensory and emotional awareness that is integral to sense-of-self and related regulatory processes.[65, 68] The neural mechanisms that underlie successful SUD treatment are not yet well understood however sensory information gained through interoception appears to play an important role in affective and regulatory behavior and successful inhibition of drug use. The role of interoception in addiction is emphasized in recent cognitive neuroscience models.[69-72] suggesting the neurobiology that may underlie interoception and influence craving, reward, impulse control and overall self-awareness among substance users.[71, 73, 74] A review of brain imaging studies supports interoceptive models for SUD, showing significantly altered regulatory processes involved in interoception among those with drug dependence relative to those without.[71] Specifically, individuals with SUD show greater activation to

drug cues within brain regions that predict relapse vulnerability.[75-77] In SUD, attention to sensory experience appears to be overly attuned substance-related stimuli, to the detriment of broader affective processing. The capacity to attend to interoceptive experience is important for the evaluation and control of visceral responses to sensory events that ultimately motivate human behavior.[73] Importantly, while unconscious interoceptive signals may motivate drug-seeking behavior,[71] interoceptive awareness is thought to reveal and de-automate such conditioning, supporting positive decision making processes critical for relapse prevention.[71]

There is compelling evidence across multiple disciplines that interoception is integral to self-regulation, including regulation of emotions and behavior.[78] Greater accuracy of interoceptive self-representation promotes adaptive responses, whereas dissociation from accurate representation can lead to dysregulation. Accordingly, addiction appears to involve interoceptive dysfunction, as do many other health problems that notably are often comorbid with addiction,[79] such as chronic pain,[80] and post-traumatic stress disorder (PTSD).[81] Given the high prevalence of relapse and poor retention in MAT treatment,[31] and the identified relapse risk factors such as stress, pain, negative affect and poor emotion regulation in SUD treatment,[75, 82] it is critical to identify interventions that promote interoceptive awareness to reduce relapse in individuals with OUD in MAT. The study of adjunctive interventions for cultivating interoceptive awareness to enhance treatment outcomes is an identified next step for SUD research.[71, 74]

Rationale for MABT as an Adjunct to MAT of OUD. Dr. Price's research focuses on an intervention, Mindful Awareness in Body-oriented Therapy (MABT), designed to teach interoceptive awareness. Findings from this program of research (including prior R21DA024771 and ongoing R01DA033324) highlight the role of improving interoceptive awareness through MABT to reduce substance use and improve health outcomes. This research indicates that avoidance of body sensations (emotional or physical) is common among individuals in SUD treatment.[83-85] In addition, maintaining attention to one's body sensations often exceeds these individuals' perceived capacities. Dr. Price's SUD research to date has focused on MABT as an adjunct to abstinence-based treatment for individuals using various primary substances (i.e., alcohol, amphetamines, opioids, etc.). Thus the proposed study patient characteristics and MAT program/setting are distinctly different from the sample and program/setting in prior MABT SUD studies (NIDA-funded R21 and R01). While psychiatric comorbidity is expected to be similar among past MABT study samples and the proposed study sample, co-morbid chronic pain is expected to be highly prevalent which it was not in prior SUD MABT studies. Likewise, the setting/treatment programs are distinctly different, involving regular visits to a medical setting for medication-assisted treatment but without the group psychoeducational program that defines intensive outpatient abstinence-based treatment. Also, while the results from a pilot study of Mindful Awareness in Body-oriented Therapy (MABT) for veterans with PTSD and comorbid chronic pain,[86] demonstrated the acceptability of MABT for chronic pain patients and the perceived positive impact on pain management, the study was not sufficiently powered to see changes on health outcomes. This proposal thus represents a next step in Dr. Price's research program to examine MABT specifically for individuals in office-based medication-assisted treatment for OUD, aligning with Stage II research to study for

whom and in what contexts this intervention may be beneficial;[87] this would be the first MABT SUD study to include men and the first MABT study sufficiently powered to examine the effect of MABT on individuals with comorbid chronic pain.

2.2 Study Rationale

Mindful Awareness in Body-oriented Therapy as an Adjunct to SUD Treatment. Prior NIDA-funded studies of MABT for SUD treatment provide an empirical basis for the design and methods of the current proposal. The results of prior study (R21) comparing MABT+TAU to TAU only (N = 46) and results from recently completed study (R01) of MABT comparing MABT+TAU to TAU only and Women's Health Education (to control for time and attention) (N = 217) in women's SUD treatment are summarized below. Both studies used the manualized MABT protocol, to be implemented in the proposed study. Dr. Price's experience developing, implementing, and disseminating results of previous MABT studies provide a logical and tested background for this research.

MABT Implementation as an Adjunct to Community - Based SUD Treatment: MABT implementation as an adjunct to SUD treatment is highly acceptable to patients and staff at community treatment facilities.[88] Dr. Price's R01 was implemented in three community SUD clinics in the Seattle area, the vast majority of participants are very low SES (85% unemployed, 87% on Medicaid or Medicare, and 43% highest level of education was high school), similar to the characteristics we expect in the proposed sample.[89]. Likewise, comorbid mental health distress in the R01[89] and prior R21,[85] particularly PTSD (68%) and depression (34% with moderate – severe symptoms), is comparable to what is expected in the proposed study sample (see Section 4).

MABT Reduces Substance Use Outcomes: MABT SUD treatment research (R21 study) showed significant reduction in substance use for MABT+TAU as measured by the percent days abstinent (primary outcome) on the Time Line Follow-Back Interview (TLFB) compared to TAU only.[85] R01 findings (N =187) show significant reductions in the percent days abstinent (also using the TLFB as primary outcome) in MABT+TAU compared to TAU only at 6 month and 12 month follow-up.[90]

MABT Reduces Psychological Symptoms and Improves Emotional Well-being, Mindfulness, and Interoceptive Skills: MABT SUD treatment research (R21 study) showed promising results with significant between-group differences with moderate to large effects on mental health outcomes between MABT+TAU compared to TAU at 9 months. These included depression symptoms, eating disorder symptoms, perceived stress, dissociation, and physical symptom frequency.[85] The R01 pre-post findings (N = 187) showed significant improvements for MABT compared to TAU in craving, depression among those that received the full intervention dose, improved emotion regulation (self-report and psychophysiology), interoceptive awareness, and mindfulness skills among the MABT completers.[89]. Longitudinal outcomes showed maintained improvements for MABT vs. TAU on craving, psychophysiology (well-being/regulation), interoceptive awareness and mindfulness skills.[90] The proposed study examines many of the same mental health and process variables as in the above studies.

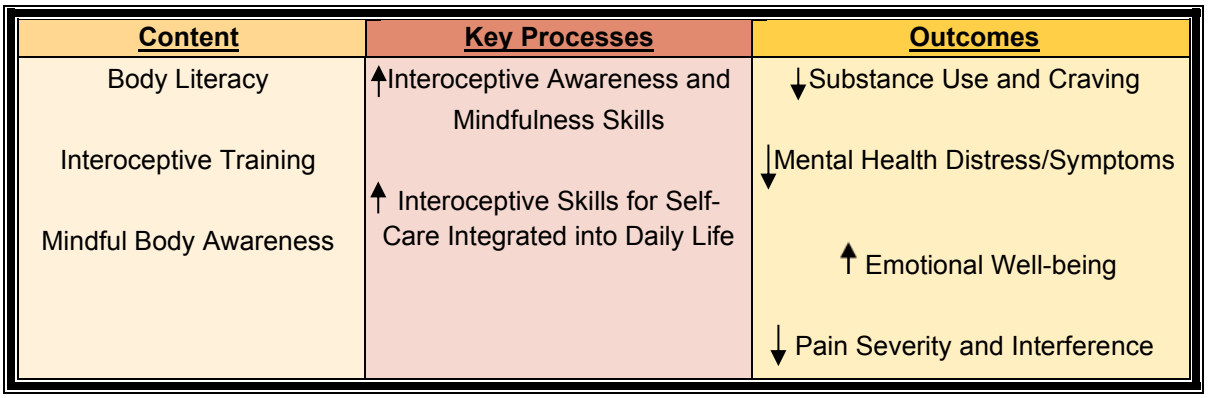
Patients on MAT frequently suffer from chronic pain, which is a risk factor for opiate craving

and potential relapse. We conducted a cross-sectional study (K23DA027367) of 106 adults who were maintained on buprenorphine or methadone.[91] The primary outcome was cold pain tolerance assessed by cold-pressor test. Chronic pain was highly prevalent (67%), and current pain was even moreso (83%). These results reinforced that pain and hyperalgesia are common problems in this population of persons who were maintained on MAT for treatment of OUD. In a subsequent study performing secondary analysis on data from the same sample, we examined relationships between pain and opioid craving and opioid use as measured by urine drug testing (UDT).[92] We found that 51% reported craving opioids in the past week, and 16% had a positive UDT for opiates. We concluded that chronic pain with associated opioid craving potentially places this population at risk for relapse. Results from these two studies underscore that there is an unmet need for interventions to address pain among persons on MAT in order to prevent relapse and improve addiction treatment outcomes.

In summary, these preliminary studies demonstrate that MABT reduces substance use and comorbid mental health distress among women in abstinence-based SUD outpatient treatment, suggest that the MABT intervention can restore interoceptive function in the face of SUD, and point to the importance of addressing chronic pain in MAT for OUD. However, MABT has not yet been examined as an adjunct to MAT with an exclusively OUD sample nor have MABT studies included targeted pain outcomes, crucial to address the need for nonpharmacological supports for MAT treatment during this opioid epidemic. Furthermore, MABT has not been studied in a more generalized sample of women and men. This study is designed to accomplish these critical next steps.

Mindful Awareness in Body-Oriented Therapy. The MABT protocol and training manual teaches interoceptive awareness and self-care skills for emotion regulation to facilitate improved health outcomes (see Explanatory Model, Figure 1 below).

Figure 1. MABT Explanatory Model



MABT involves delivery of eight 75-minute one-on-one sessions, once per week. MABT is distinctive in its explicit focus on the development of interoceptive awareness skills for emotion regulation. Strategies for addressing interoceptive dysfunction are not well developed in typical group mindfulness-based approaches of individual psychoeducational approaches that include a somatic focus. To address this issue, MABT provides an individualized protocol for scaffolding interoceptive awareness in the face of baseline

difficulty in attending to interoceptive signals, through a combination of psychoeducational and somatic approaches explicitly addressing difficulties with interoceptive processing. Used in multiple clinical trials,[83, 85, 86, 93-95] the protocol has an incremental approach for teaching interoceptive awareness to facilitate development of interoceptive awareness skills (see Table 2).

Table 2. Key MABT Elements *(number of minutes each session)*

Stage 1 (Sessions 1- 2)	Stage 2 (sessions 3-4)	Stage 3 (sessions 5-8)
Check-in (20)	Check-in (20)	Check-in (20)
Massage/Body Literacy (40)	Massage/Body Literacy (10)	Massage/ Body Literacy (10)
	Interoceptive Training (30)	Mindful Body Awareness (30)
Session Review (15)	Session Review (15)	Session Review (15)
Homework	Homework	Homework

The MABT intervention is designed to increase self-awareness and thus participants sometimes experience discomfort, emotions, as well as insight. Overall MABT is very low risk, as the protocol is designed to be individualized to ensure safety and comfort of the participant. To date, here have been no serious adverse events associated with any MABT study.

For participants initially assigned to MABT who report continued use of opiates or other substances at 6 months, an additional 6 MABT sessions will be offered.

3. STUDY DESIGN

Design Overview: A two-group (n = 165/165), randomized, repeated measures design will be employed. Three hundred thirty individuals with OUD engaged in medication treatment will be recruited at one of five outpatient treatment sites: Harborview Medical Center, Country Doctor Community Health Centers, North Olympic Healthcare Network, Cascade Medical Advantage, and Evergreen Treatment Services. Enrolled patients will be individually randomized within sites to receive MABT+TAU (experimental group), or TAU alone (control). Assessments will be administered at baseline, post-intervention (3 months from baseline), and at 6, 9 and 12 months follow-up. An additional six sessions of MABT will be offered to those randomized to MABT who have continued substance use at six months.

Randomization: Following baseline data collection, participants will be randomized to treatment group by the Research Coordinator. Dr. Pike, the project statistician, provided a randomization program programmed in Microsoft BASIC. Randomization will be specific to each study site and stratified by sex (approximately equal numbers of men and women assigned to each study group at each site) and baseline self-reported chronic pain. The algorithm used for randomization is a modification of a minimization method[96] based on an overall imbalance score which measures how far out of balance (within strata) the study is for a given set of random assignments. Participants will be informed of their assignment within one week of the initial appointment. Prior MABT studies showed no loss due to randomization to treatment group, thus we do not expect randomization to precipitate significant attrition. The Research Coordinator at each facility will not be blind to condition and will inform participants of their treatment condition and MABT therapist.

Measures: The outcome measures are described below (see also Table 1 in Précis).

Primary Objectives: The primary outcome is patient-reported days of illicit opioid use. Self-reported substance use is the recommended approach for intervention studies.[97] Days of illicit opioid use is defined as the number of reported days of use in last 90 days (baseline assessment) or since and including the last assessment date (follow-up assessments) in which opioids other than MAT (buprenorphine or methadone) are reported.

Time-Line Follow-Back Interview (TLFB)[3, 4] will be used to assess opioid use, other illicit drugs, and commonly abused prescription medications. Participants will be asked first to identify what substances were used. The participant will then be asked to use a calendar to retrospectively estimate their substance use, for each of the identified substances. The TLFB method was determined for alcohol, amphetamines, cannabis, cocaine, hallucinogens, opiates, sedative-hypnotics, and any psychoactive substance for time periods of 0-30 days, 0-90 days, and 0-365 days, the correlations for all substances and for the three time periods ranged from .73 to .95, demonstrating test-retest reliability and validity.[98]

The secondary outcome is days of other illicit substance use is defined as the number of days since last assessment in which cocaine, amphetamine/methamphetamine, hallucinogens, non-prescribed benzodiazepines or barbiturates, or alcohol heavy drinking days are reported using the TLFB. We will not include cannabis in this primary outcome measure due to its legal status in Washington State.

Secondary Objective Outcomes: measures of mental health (distress symptoms and emotional well-being) will include three well-validated scales for diagnostic screening: the 9-item PHQ-9 to screen for depression, the 7-item (α =.92) GAD-7 for anxiety[8], and the Posttraumatic Stress Disorder Checklist for *DSM-5* (PCL-5),[9] which assesses symptoms of post-traumatic stress on a Likert-type scale with 20 items (α =.94). The 4th measure, the Difficulty in Emotion Regulation Scale short form (DERS-SF)[10, 99] assesses difficulties in the modulation of emotional arousal. There are 18 items on a Likert-type scale (DERS α =.93; DERS short form α ranges from .78 to .91 with original DERS subscales) and four subscales that assess the degree of awareness, understanding, and acceptance of emotions, and the ability to act in desired ways regardless of the emotional state. The 5th and 6th measures, the Freiberg Mindfulness Questionnaire (FMQ) with 14 items[14], and the Multidimensional Assessment of Interoceptive Awareness (MAIA)[15] with 32 items on a Likert-type scale, are used to assess skills learned in the intervention.

Physical symptoms will be assessed using the Medical Symptoms Checklist (MSC) and pain severity and interference using the Brief Pain Inventory (BPI). The MSC measures the frequency (0-8 scale) and severity (0-10 scale) of 29 common physical symptoms.[19] The BPI is a validated, widely used measurement tool for assessing clinical pain. In the U.S. it has been validated in non-cancer patients with pain[18] and HIV-infected patients.[100] The assessment includes 13 questions which provide information on pain severity and pain interference in the past week. Participants are initially asked if they have experienced any significant pain in the past week, and if they respond positively they answer subsequent

questions about duration of pain, pain severity and interference. Pain severity is rated from 0 ("no pain") to 10 ("worst pain imaginable"), and participants are asked to rate their current pain as well as pain at its worst, at its best, and on average in the past week. Pain interference includes information on the impact of pain on general activity, walking, work, mood, enjoyment of life, relations with others, and sleep, asking the participant to rate interference on a scale from 0 ("does not interfere") to 10 ("completely interferes"), and is reported as the mean of seven questions. Participants who responded that they had no pain in the past week will be coded "0" for pain severity and interference. The BPI will be supplemented with a single question on duration of currently reported pain in order to establish whether the pain is acute or chronic.

Opioid craving will be assessed using a single item numeric scale.[5] Participants are asked: "On a scale of 0–10, please indicate how much craving you have experienced during the past week," with responses anchored at "0=no craving at all" and "10-strongest craving ever". Retention will be defined as days retained in the program, or time to program discharge. Program discharges are documented in the electronic medical record (EMR) and date of discharge will be extracted from the record.

R01-Specific Objective 3 Outcomes: Exploration of the effectiveness of additional MABT dose offered at 6 months to those with continued substance use compared to those with continued substance use at 6 months in the TAU will be assessed using the Time-Line Follow-Back Interview (TLFB)[3, 4] self-reported substance use as described in in the primary objective.

For description of the intervention, see Section 2.2.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

Study Population: We plan to enroll 330 patients entering treatment for OUD at the three identified clinical sites. We expect the clinical characteristics of study subjects to be similar to those in enrolled in the SAMHSA MAT-PDOA project (see Table 3).[101] The patients at the two clinics have near equivalence in the numbers of men and women served, and age range (18 - 70 years old) with the majority (59%) under the age of 35. Most patients are white, low-income, have at most a high school education, and are on public insurance (Medicare or Medicaid), with substantial mental health and substance use co-morbidity. Approximately 25% are minorities.

Table 3. Description of Enrolled Patients in WA-MAT-PDOA Program (n=400)	
Male	55%
Age, Mean	36.9
White, Non-Hispanic	78%
Mod-Severe Depression (PHQ9>10)	67%
Mod-Severe Anxiety (GAD7>10)	62%
Mod-Severe PTSD (PCL>29)	56%

Past 30-Day:	
Cannabis Use	**37%**
Alcohol Use	22%
Opioid Use	70%
Illicit Rx Opioid Use	39%
Heroin Use	47%
Injection Drug Use	31%
Employed or Student	31%
Housed	91%
Criminal Involvement*	12%
*Arrests, Probation/Parole, Jailed, Sentencing	

4.1 Inclusion Criteria

Candidates for participation must meet all of the following criteria to participate in the study. Participants must be: 1) diagnosed with OUD, 2) enrolled in a medication treatment program for opioid use disorder, 3) over 18 years old, 4) enrolled and is stable in program involving (to assure medication initiation/induction has occurred) involving (if on buprenorphine) at least 4 weeks of treatment (to assure medication initiation/induction has occurred) and Rx appointments are less frequent than once/week, and (if on methadone) at least 90 days in treatment with a minimum dose of 60mg, no missed dose evaluation appointments in past 30 days, and no more than 3 missed doses in 30 days, 5) willing to forego (non-study) manual (e.g., massage) and/or mind-body therapies (e.g., mindfulness meditation) for 3 months (baseline to post-test); 6) willing to sign release for access of electronic medical records; 7) fluent in English; 8) able to attend study sessions when offered.

4.2 Exclusion Criteria

Candidates meeting any of the following criteria at baseline will be excluded from study participation. Participants must not be: 1) unwilling or unable to remain in medication treatment for OUD for the duration of the trial (includes planned relocation, pending incarceration, planned surgical procedures, etc.); 2) over 24 weeks gestation or unknown gestation, if pregnant; 3) noted by clinical or study staff as showing overt psychosis or other conditions such as cognitive impairment; cognitive impairment to be assessed with an adapted 7-item Mini-Mental Status Exam (MMSE),[102] a common screening tool in SUD treatment studies,[103] if there is questionable difficulty comprehending the consent.

4.3 Study Enrollment Procedures

Recruitment: Patients enrolling in MAT at the study sites will be recruited for study participation. Flyers with information about the trial will be distributed to clinicians and staff working with patients in medication treatment for OUD. The Nurse Care Manager(s) or

Providers at each site, who see patients in the program on a weekly basis at the start of treatment, will identify patients who meeting basic eligibility criteria, and will distribute the recruitment flyer to these participants at the time of their visit while also providing the patient with a brief overall study description and an opportunity to ask questions.

The flyer will explain that study participation involves randomization to one of two study conditions, and that one of these conditions involves receiving an 8 session intervention with a focus on body awareness, mindfulness skills, and self-care. Patients interested in study participation will be asked by the clinical staff to for permission to be contacted by the Research Coordinator (RC). The clinical staff will provide the RC with documentation with each referral that the patient meets basic eligibility criteria for study involvement (e.g. diagnosed with OUD and stable on medication dose). Based on prior intervention study experience at community SUD treatment facilities and the pilot for this study, we expect to recruit 8-12 participants per month across the sites. This recruitment rate would allow us to complete recruitment within the projected timeline. Assignment to study groups will involve stratification by sex and chronic pain (approximately equal numbers at each site) to ensure parity between men and women, and to ensure an equal distribution by group on chronic pain.

Screening: The Research Coordinator (RC) at each site will screen interested patients for eligibility in-person at the time of referral (if available) or by phone using a standardized screening script that includes acquiring verbal consent to collect preliminary screening data. On conclusion, the results of screening interview (eligibility based on inclusion/exclusion criteria, election of participation) will be entered into the screening log of the study database. Candidates who are eligible and willing to continue will be scheduled for an initial assessment visit within 14 days of the screening.

Consent and Enrollment: The initial scheduled in-person visit includes the informed consent process during which candidates will be asked to read the consent form (or if preferred, have it read to them), after which the RC will verbally reaffirm major points (participation is voluntary, potential risks, randomization protocol, etc.) and elicit and answer any questions from the candidate. If the candidate provides written consent, then the enrollment process will continue with the baseline data collection. Upon completion of the initial assessment, participants will be enrolled in the study. If at any time during this process the candidate withdraws prior to enrollment, disposition and reason for withdrawal (if obtainable) will be documented in the screening log.

Randomization: Following baseline data collection, participants will be randomized to treatment group. Dr. Pike, the project statistician, provided a randomization program programmed in Microsoft BASIC. Randomization will be specific to each study site and stratified by sex (approximately equal numbers of men and women assigned to each study group at each site) and baseline self-reported chronic pain. The algorithm used for randomization is a modification of a minimization method[96] based on an overall imbalance score which measures how far out of balance (within strata) the study is for a given set of random assignments. Dr. Pike, who will have no contact with study participants, programmed

the site-specific random assignment generators so that assignments become known to the Research Coordinator only upon entry of the eligibility data. Prior MABT studies showed no loss due to randomization to treatment group, thus we do not expect randomization to precipitate significant attrition. The Research Coordinator at each facility will not be blind to condition and will inform participants of their treatment condition and MABT therapist.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

The intervention in this study is Mindful Awareness in Body-oriented Therapy (MABT), administered one-on-one by therapists trained in the MABT protocol at the outpatient treatment site where the participant was recruited from and receives their MAT care. Individuals in the MABT intervention group will receive 8 weekly 1.25 hour one-on-one sessions of MABT between baseline and the 3 month follow-up assessment. There are no restrictions to supportive care, medications, or other treatments which intervention group participants may use during their participation in the study with the exception of additional manual (e.g., massage) and/or mind-body therapies of meditation and yoga during the first three months of study engagement (this information is part of the screening process for enrollment, and will be reiterated by the research coordinator at the time of study enrollment). There are no anticipated adverse effects of the intervention other than the possibility of short-term emotional discomfort.

At six months, those in the MABT treatment group with continued substance use will be offered an additional six sessions of MABT between the 6 month and 9 month assessments.

5.2 Handling of Study Interventions

Mindful Awareness in Body-oriented Therapy (MABT): The MABT intervention has a well-developed protocol and training manual for research. Used in multiple clinical trials,[83, 85, 86, 93-95] the protocol has an incremental approach for teaching interoceptive awareness skills and developing weekly individualized homework based on session content to promote integration of practice into daily life. Individuals in the MABT treatment group will receive 8 weekly 1.25 hour one-on-one sessions of MABT. Research therapists will be hired and trained to provide the MABT intervention. MABT has three distinct stages (see Table 2). Stage 1 (sessions 1–2), develops body literacy, the ability to identify and articulate sensory awareness. Body literacy training is done in the context of massage therapy to facilitate sensory awareness related to attention to the quality of soft tissue (e.g., muscular tension). Stage 2 (sessions 3–4) focus on interoceptive awareness training to develop the ability to access inner body awareness and begin to make links between physical and emotional sensations. Stage 3 (sessions 5–8) focuses on the development and practice of mindful body awareness involving sustained interoceptive attention which facilitates positive shifts in sensory experience as well as insights that motivate behavior change. Each session begins with a semi-structured check-in to build trust and familiarity between therapist and participant, and ends with session review to facilitate cognitive integration of the session

material and to collaboratively develop the homework for the interim week. The interoceptive training components (stages 1–3) are designed with an incremental approach to facilitate learning, particularly important for individuals with SUD who often have difficulties attending to sensory (physical and emotional) awareness. Individualized homework is based on session content and crafted to promote integration of practice into daily life.

The additional six MABT sessions that will be offered to eligible participants at 6 months will be delivered as explained above and will include all stages of the intervention as outlined in Table 2 but will be individualized to address the intervention components needing the most review (if the participant did not complete MABT initially) or will follow the intervention protocol for delivery of the first 6 of 8 sessions if the received no prior MABT sessions when initially assigned.

A single therapist works with each study participant for MABT delivery. In case of illness or vacation, on the part of either participant or interventionist, the intervention period allows for approximately 12 weeks to deliver an 8 week intervention. Any longer-term breaks needed in interventionist coverage/ staff turnover will be handled by having a trained therapist ready to step-in if needed, either to provide temporary coverage (i.e. to work with one set of 3-4 participants over 2-3 months to deliver a full set of MABT sessions) or to join the research team more permanently.

Treatment As Usual: All participants will continue to receive usual outpatient treatment at the site from which they were recruited. The outpatient programs at these sites are comparable; they offer medication treatment provided by a Medical Provider or through a Nurse Care Manager (NCM) model adapted from the Massachusetts Model as piloted in the MAT-PDOA program. The model uses Nurse Care Managers (NCM) as the hub of the medical care team to coordinate and manage patients. The use of the NCM addresses many barriers to medication prescribing that physicians face. For example, treatment for opioid use disorders with buprenorphine/naloxone (BUP/NX) is time-intensive in the first 2-3 months. Clinical steps which the NCM assists include: an initial screening for the appropriateness of BUP/NX; a comprehensive assessment of substance use and consequences, medical and mental health, and current barriers to and supports for recovery; review for formal diagnosis of opioid use disorder and appropriateness for MAT; scheduling and monitoring of the induction (i.e., initiation of BUP/NX which must be accomplished while patients are in withdrawal), followed by weekly visits for prescriptions, and urine drug testing for the first 1-2 months (less frequent thereafter if patients are abstaining). Frequent team meetings with the physician, NCM and program manager occur, during which team members can monitor progress and update treatment plans together. Counseling is available for all patients, but not required.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

Participants will all be enrolled in MAT for the duration of the study. Participants are welcome to engage in optional counseling or attend peer support meetings such as 12-step groups, as this is considered part of treatment as usual (TAU). If a participant withdraws

from MAT during the study, we will continue to follow them (per intent to treat); in all cases, we will collect information on any related treatment activities engaged in during the study period.

5.3.2 Required Interventions

The participants must have received their fourth weekly MAT prescription to be enrolled in the study. Per intent-to-treat design, study participation is not contingent on continued adherence to MAT treatment once enrolled in the study.

5.3.3 Prohibited Interventions

There are no restrictions to supportive care, medications, or other treatments which participants may use during their participation in the study with the exception of additional manual (e.g., massage) and mind-body therapies (specifically yoga and meditation) from baseline to 3 months. To assess whether participants adhere to this exclusion, or utilize these therapies later in the study, participants will asked about their receipt of massage or participation in any yoga or meditation classes at each assessment.

5.4 Adherence Assessment

To assess adherence to the study intervention we will record number of sessions attended. In addition to an intent-to-treat analysis, we will also examine MABT dose. Specifically, we will examine outcomes for participants who attended > 75% of the initial intervention sessions (i.e. 6-8 sessions) between baseline and 3 months, as this is the number of sessions needed in order to receive all intervention components, compared to TAU. We will also record the number of additional sessions received by eligible participants between 6 and 9 months.

6. STUDY PROCEDURES

6.1 Table 4. Schedule of Evaluations

Assessment	Screening: Visit or Call (Day -14 to Day -1)	Baseline, Enrollment, Randomization: Visit 1 (Day 0)	Treatment Visit 1 (W1)	Treatment Visit 2-8 (W2 - 11)	Followup1: Post-Treatment Visit (W12)	Followup2: Visit (W24)	Booster Treatment Visits 1-6 (W25 - 38)	Followup2: Visit (W39)	Followup2: Visit (W52)
Screening Questions	X								
Inclusion/Exclusion Criteria	X								
Informed Consent Form		X							
Demographics and Health History		X							
Trauma History (TLEQ)		X							
REDCap Survey		X			X	X		X	X
Treatment Adherence (Retention to MAT)						X			X

Assessment	Screening: Visit or Call (Day-14 to Day -1)	Baseline, Enrollment, Randomization: Visit 1 (Day 0)	Treatment Visit 1 (W1)	Treatment Visit 2-8 (W2 - 11)	Followup1: Post-Treatment Visit (W12)	Followup2: Visit (W24)	Booster Treatment Visits 1-6 (W25 - 38)	Followup2: Visit (W39)	Followup2: Visit (W52)
Economic Indicators (Employment, Health Utilization, Legal Status)		X			X	X		X	X
Toxicology screen		X							
Enrollment/Randomization		X			X	X		X	X
MABT Process Evaluation			X	X			X		
Adverse Events			X	X	X	X	X	X	X

6.2 Description of Evaluations

6.2.1 Screening Evaluation

Consenting Procedure

The Research Coordinator (RC) at each site will acquire verbal consent to ask screening questions to determine eligibility prior to beginning screening procedures. Written consent will be obtained for all further study procedures as described in section 6.2.2.

Screening

After acquiring consent to screen, the RC at each site will screen interested patients to determine eligibility in-person at the time of referral (if available) or by phone using a standardized screening script. On conclusion, the results of screening interview will be entered into the screening log of the study database. Results are 1) eligibility based on inclusion/exclusion criteria, 2) if eligible, election of participation (if no, reason why not), 3) if not eligible, reason for ineligibility. Candidates who are eligible and willing to continue will be scheduled for the consent /initial assessment visit within 14 days of the screening, or be rescreened prior to progressing. Eligibility, election, and follow-up information (for those who are eligible and willing to continue) will be entered in the study database.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

The first study visit will begin with the consent process. At the consent visit, the RC will ask if the candidate would like to read it themselves or have it read to them, then will give the participant time to read the consent (or read it aloud). Then the RC will paraphrase each section of the consent form, and encourage the candidate to ask questions. If the candidate wishes to proceed, they will sign and date the consent form. If there is any concern about comprehension, the RC will administer an adapted 7-item Mini-Mental Status Exam to ensure that there is not cognitive impairment.

The RC will also explain the HIPAA and Medical Records Release forms (if required by the clinical site) to acquire limited data elements from the candidate's medical record. Permission to access medical records is required for participation in the research study. A copy of the forms will be provided to the candidate. A locator form with additional contact information will also be requested, but refusal does not preclude participation in the study.

After informed consent is given, the baseline assessment is completed. On completion of the baseline assessment, the participant will be enrolled and randomized.

Completion status for the consent procedures will be entered in the study database, and signed forms filed in the candidate's name file in a locked filing cabinet, separate from numerical identifiers.

Baseline Assessments

The baseline assessment requires the participant to complete: 1) the Timeline Follow-back Interview to report on substance use over the past 90 days, 2) an online survey (REDcap) to collect a set of baseline-only questionnaires specific to demographics and health history, 3) an online survey using REDcap that collect responses to self-report outcome measures, 4) a toxicology screen involving a urine sample for biochemical evaluation. The administration of the baseline assessment is process takes approximately 1 hour. All assessments will be delivered in a standardized order as outlined below; at baseline only, there are two additional measures on the online REDcap survey

Should a participant be unable to provide data during the scheduled assessment (e.g., unable to provide a urine sample, or unable to complete the assessment in one sitting), research coordinators have up to 14 days to complete the data collection for the assessment.

Baseline, Enrollment, Randomization: Visit 1 (Day 0)
Measures:

Primary outcome:

- Time-Line Follow-Back Interview (TLFB)[3, 4] will be used to assess self-reported opioid use, and use of other illicit drugs, marijuana and alcohol use.

Demographics and health history:

- Health History Form is based on the Addiction Severity Index.[1]
- Trauma Life Events Questionnaire (TLEQ)[2] will be used to describe lifetime trauma exposure.

Secondary outcomes:

- The PHQ-9 will be used to measure depression symptoms.[6, 7].
- The GAD-7 will be used to measure anxiety symptoms.[8]
- Posttraumatic Stress Disorder Checklist for *DSM-5* (PCL-5),[9] assesses symptoms of post-traumatic stress on a Likert-type scale.

- Difficulty in Emotion Regulation Scale – short form (DERS- SF)[10] assesses difficulties in the modulation of emotional arousal.
- Opioid craving will be assessed using a single item numeric scale.[5] Participants are asked: "On a scale of 0–10, please indicate how much craving you have experienced during the past week," with responses anchored at "0=no craving at all" and "10-strongest craving ever".
- Freiberg Mindfulness Questionnaire has 14 items to assess skills learned in the intervention.[14]
- Multidimensional Assessment of Interoceptive Awareness (MAIA)[15] has 32 items on a Likert-type scale to assess skills learned in the intervention.
- Brief Pain Inventory (BPI) is a validated, widely used measurement tool for assessing clinical pain.[18] The BPI will be supplemented with a single question on duration of currently reported pain in order to establish whether the pain is acute or chronic.
- Medical Symptoms Checklist will assess self-report of physical symptoms.[19]

Descriptive Data:

- Economic Indicators questions will gather data on employment, health utilization, and legal status.
- Toxicology screen will be used to collect point prevalence for substance use on at each assessment time point, and will serve as supplemental data for validation of the TLFB results.

After the completion of the baseline assessment, the participant is formally enrolled in the study.

Randomization

Following baseline data collection, participants will be randomized to treatment group by the Research Coordinator. Randomization will be provided by the project statistician. Stratified randomization by study site, baseline self-reported chronic pain, and gender, will be used to distribute participants evenly between the two treatment conditions at each facility and within each gender and experience of chronic pain. Randomization will use a modified minimization method algorithm[96] based on an overall imbalance score which measures how far out of balance (within strata) the study is for a given set of random assignments to ensure approximately equal accrual into the two experimental arms and to facilitate concealment of treatment assignments. After randomization (for those assigned to treatment group), the RC will contact the site interventionist to inform them of their new assigned participant to schedule the first intervention visit.

6.2.3 Blinding

The statistician will be blind to study group. The RC at each facility will not be blind to condition and will inform participants of their study group condition.

6.2.4 Follow-up Visits

Treatment

Initial Treatment Visit 1 (W1)

- Adverse Events
- MABT Process Evaluation (self-report by interventionists)

Initial Treatment Visit 2-8 (W2 - 11)

- Adverse Events
- MABT Process Evaluation (self-report by interventionists)
- MABT Practice Log (self-reported home practice by participants for use by interventionists)

Additional MABT Sessions 1-6 (W25 – W38)

- Adverse Events
- MABT Process Evaluation (self-report by interventionists)
- MABT Practice Log (self-reported home practice by participants for use by interventionists)

Assessments

Followup1-4 Assessment Visits (W12, W24, W39)

The follow-up assessments will be scheduled 12 weeks, 24 weeks, and 39 weeks from baseline, and takes approximately 45 minutes to complete. Coordinators will make every effort to schedule the assessment near to the target date, but are allowed -2 weeks/+4 weeks to capture follow-up assessment data. In addition to this assessment, we will also gather treatment retention data through electronic medical record (EMR) at the 6 and 12 month assessments.

Should a participant be unable to provide data during the scheduled assessment (e.g., unable to provide a urine sample, or unable to complete the assessment in one sitting), research coordinators have up to 14 days to complete the data collection for the assessment.

W24: The Time-Line Follow-Back Interview (TLFB)[3, 4] results collected at 6 months will be used to determine those in the MABT study group with continued substance use who will be offered six additional MABT sessions between month 6 and 9. Criteria for eligibility for additional MABT sessions is 1) randomized to the MABT + TAU study group, and b) self-report of substance use on the TLFB, including any days of heavy alcohol drinking and excluding marijuana use.

Primary outcome:

- Time-Line Follow-Back Interview (TLFB)[3, 4] will be used to assess self-reported opioid use, and use of other illicit drugs, marijuana, and alcohol.

Secondary outcomes:

- The PHQ-9 will be used to measure depression symptoms.[6, 7].
- The GAD-7 will be used to measure anxiety symptoms.[8]
- Posttraumatic Stress Disorder Checklist for *DSM-5* (PCL-5),[9] assesses symptoms of post-traumatic stress on a Likert-type scale.
- Difficulty in Emotion Regulation Scale – short form (DERS- SF)[10] assesses difficulties in the modulation of emotional arousal.
- Opioid craving will be assessed using a single item numeric scale.[5] Participants are asked: "On a scale of 0–10, please indicate how much craving you have experienced during the past week," with responses anchored at "0=no craving at all" and "10-strongest craving ever".
- Freiberg Mindfulness Questionnaire has 14 items to assess skills learned in the intervention.[14]
- Multidimensional Assessment of Interoceptive Awareness (MAIA)[15] has 32 items on a Likert-type scale to assess skills learned in the intervention.
- Brief Pain Inventory (BPI) is a validated, widely used measurement tool for assessing clinical pain.[18] The BPI will be supplemented with a single question on duration of currently reported pain in order to establish whether the pain is acute or chronic.
- Medical Symptoms Checklist will assess self-report of physical symptoms.[19]

Descriptive Data:

- Economic Indicators questions will gather data on employment, health utilization, and legal status.
- Biochemical drug screen will be used to collect point prevalence for substance use on at each assessment time point, and will serve as supplemental data for validation of the TLFB results.
- Adverse Events

6.2.5 Completion/Final Evaluation

Followup2: Final Visit (W24)

The final evaluation (12 month follow-up) will be scheduled 52 weeks from baseline, and takes approximately 45 minutes to complete. Coordinators will make every effort to schedule the assessment near to the target date, but are allowed -2 weeks/+4 weeks to capture final assessment data. In addition, to this assessment, we will also gather treatment retention data through electronic medical record (EMR).

Should a participant be unable to provide data during the scheduled assessment (e.g., unable to provide a urine sample, or unable to complete the assessment in one sitting), research coordinators have up to two weeks to complete the data collection for the assessment.

If study staff learn of special circumstances that would necessitate collecting W24 data earlier than the allowed window of -2 weeks (e.g., expected relocation, incarceration, etc.), the

assessment will be completed early and the participant followed to determine if a repeat assessment within the allowable window is possible. If so, the final assessment will be repeated and the later data used in the final analysis. Participants will be remunerated for the second W24 assessment.

Primary outcome:

- Time-Line Follow-Back Interview (TLFB)[3, 4] will be used to assess self-reported opioid use, and use of other illicit drugs, marijuana, and alcohol.

Secondary outcomes:

- The PHQ-9 will be used to measure depression symptoms.[6, 7].
- The GAD-7 will be used to measure anxiety symptoms.[8]
- Posttraumatic Stress Disorder Checklist for *DSM-5* (PCL-5),[9] assesses symptoms of post-traumatic stress on a Likert-type scale.
- Difficulty in Emotion Regulation Scale – short form (DERS- SF)[10] assesses difficulties in the modulation of emotional arousal.
- Opioid craving will be assessed using a single item numeric scale.[5] Participants are asked: "On a scale of 0–10, please indicate how much craving you have experienced during the past week," with responses anchored at "0=no craving at all" and "10-strongest craving ever".
- Freiberg Mindfulness Questionnaire has 14 items to assess skills learned in the intervention.[14]
- Multidimensional Assessment of Interoceptive Awareness (MAIA)[15] has 32 items on a Likert-type scale to assess skills learned in the intervention.
- Brief Pain Inventory (BPI) is a validated, widely used measurement tool for assessing clinical pain.[18] The BPI will be supplemented with a single question on duration of currently reported pain in order to establish whether the pain is acute or chronic.
- Medical Symptoms Checklist will assess self-report of physical symptoms.[19]

Descriptive Data:

- Economic Indicators questions will gather data on employment, health utilization, and legal status.
- Biochemical drug screen will be used to collect point prevalence for substance use on at each assessment time point, and will serve as supplemental data for validation of the TLFB results.
- Adverse Events

Withdrawal of Participants

MABT sessions will be discontinued for any of the following three reasons, but not withdrawn from study (e.g., participant will be continued to be followed for study assessments):

1. Participants are inebriated or high from alcohol or drugs such that they are not able to engage in the intervention on more than one scheduled session.
2. If, in consultation with the participant's healthcare providers, there is concern for his/her safety and well-being (e.g., escalation of symptoms).

A participant could be withdrawn from study if:

If, in consultation with the participant's health care providers, there is sufficient concern for his/her safety and well-being that the participant may be withdrawn and re-directed to more appropriate care. This is described to the participant in the consent process.

If a participant chooses to formally withdraw from the study by notifying the principal investigator, any data collected from the participant will not be used in the analysis.

7. SAFETY ASSESSMENTS

7.1 Specification of Safety Parameters

It is possible that participants may experience anxiety related to questions asked on the questionnaires. For participants who receive MABT, there may be anxiety due to the use of touch in the MABT sessions or the development of a new therapeutic relationship. During the course of the study, interventionists may develop concerns regarding a participant's risk of suicide or harm to self or others, or health concerns such as increased medical symptoms such as pain, or mental health symptoms of severe depression, anxiety, PTSD. Upon entering the study, all participants will be asked to sign a Treatment Information Release Form, which will allow for two-way communication between research and clinical staff to discuss concerns such as those described.

Any medical emergencies, disclosed suicidal ideation, or other urgent concerns for participant safety experienced by the research coordinators or interventionists will be addressed according to the procedures at the clinical site where the participant is seen. Review of these protocols and accessing emergency contact information will be included in the staff training for all study staff. The study staff with the experience will report the event and resolution/follow-up to the principal investigator(s) that day.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

The pilot project for this study was found to impart minimal risk by the University of Washington IRB, and the protocol for the full trial will be based on the pilot study. Few to no

study-related adverse events are expected. Prior studies of MABT showed no serious adverse events.[83, 85, 86, 89, 93, 94, 104]

7.3 Adverse Events and Serious Adverse Events

For this study, the following standard AE definitions are used:

Adverse event: An adverse event (AE) is any untoward medical occurrence in a subject during participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these

Serious Adverse Event: A serious adverse event (SAE) is any AE that results in one or more of the following outcomes:

- Death
- A life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly or birth defect
- An important medical event based upon appropriate medical judgment

AEs are graded according to the following scale:

Mild: An experience that does not have a major impact on the patient (e.g., is transient, requires no special treatment or intervention, does not generally interfere with usual daily activities). This includes transient laboratory test alterations.

Moderate: An experience that causes the patient some minor inconvenience, but is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes laboratory test alterations indicating injury, but without long-term risk.

Severe: An experience that causes a substantial disruption to the patient's well-being (e.g., requires therapeutic intervention). The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment it becomes an SAE.

The study will use a form specifically for collection of AEs. AEs will be solicited at all participant followup assessment visits with the RC and collected at all intervention visits by the Interventionists. The AE form will have the following attribution scale:

Not related: The AE is clearly not related to the study procedures (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).

Possibly related: An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.

Related: The AE is clearly related to the study procedures.

We will follow the definition and rules for reporting for **unanticipated problems** as required by the UW IRB. An "unanticipated problem" is a problem or event that meets all of the following criteria:

1) Unexpected – The harm (or potential harm) is inconsistent with risk information previously reviewed and approved by the IRB in terms of nature, severity, or frequency as well as the characteristics of the study population.
2) Related or probably related to participation in the research. Probably related: There is a reasonable probability (more likely than not) that the incident, experience or outcome may have been caused by the procedures involved in the research, or that it is associated with the use of any drug, biologic, or medical device that is part of the research.
3) Suggests that the research places (or could have placed) subjects or others at a greater risk of harm than was previously known or recognized.

Unanticipated problems will be reported within the timeframe required by UW IRB (10 business days).

7.4 Reporting Procedures

AE Reporting and Follow-up

During the post-intervention and follow-up assessments, the Research Coordinator will inquire about AEs and complete a participant event form (PEF) if an AE is reported. Likewise, MABT Interventionists will complete a PEF form if an AE is reported during check-in's prompted in the intervention protocol. PEF forms will be submitted to the project manager weekly, and all adverse events, with the exception of clinically insignificant events and minor common illnesses and injuries (e.g., cold/flu, scrapes, upset stomach, low-grade headaches) will be documented on an AE Log and will be reported every 2 weeks to the contact PI, who provides the grading and attribution evaluation. AEs will be summarized and discussed monthly amongst the core research team. AE summary reports will be provided quarterly to the independent monitor (IM), and to the NCCIH at the time of the annual progress report. Reports will provide information on cumulative incidents and if in total the events suggest that subjects or others are at greater risk, investigators and the IM will address whether or not the consent form needs to be changed. In the annual AE summary, the Independent Monitor Report will state that he has reviewed all AE reports. If an AE/SAE meets the criteria of unanticipated problem for the UW IRB, it will be reported within 10 business days. Breach in confidentiality will reported to the IRB within 24 hours.

SAE Reporting

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the IM and NCCIH in accordance with requirements.

- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NCCIH Program Officer within 7 days. Other serious and unexpected AEs related to the intervention will be reported to the NCCIH Program Official within 15 days.

- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the IM and NCCIH in accordance with their requirements.

7.5 Follow-up for Adverse Events

During the study, participants will be attending an outpatient treatment program for OUD where they can be monitored and have access to clinical staff. Thus, AEs will be managed in conjunction with OUD treatment program staff, with permission from the participant. If a participant is no longer involved in opioid use disorder treatment, AEs will be managed by the research staff; however, if danger to self or others is identified, crisis intervention procedures will be initiated that may include referral or contacting community mental health emergency services.

7.6 Safety Monitoring

Given the IRB-determined minimal risk and early Phase II nature of the research, there will be no Data Safety Monitoring Board or Independent Monitoring Committee. Independent safety and data oversight will be provided by the Independent Monitor (IM) James Walsh M.D., an independent physician and appropriate expert with relevant expertise for advising the study investigators. He is qualified to review the patient safety data generated by this study because of his unique expertise in the area of opioid use disorder treatment as the Medical Director of the Addiction Recovery Service in a local medical system, Swedish Medical Center.

The IM will meet with the study team at the start of each study year to get an overview of the study, study implementation expectations, and study progress; and will receive quarterly brief reports detailing subject accrual, enrolled subject status and adherence, and AE/SAE summaries, and more frequent reporting by request if concerns arise. A DSM annual summary report will be provided to the IM in conjunction with required annual reporting to the IRB and NCCIH, which will detail monthly recruitment, enrollment, and retention against milestones; participant adherence, AE/SAE summary, and any other safety-related study information (e.g., serious non-compliance). Annual report tables will be generated only from aggregate (not by group assignment) baseline and aggregate safety data for the study population.

8. INTERVENTION DISCONTINUATION

MABT sessions will be discontinued for any of the following reasons, but participant will not be withdrawn from study:

1. Participants are inebriated or high from alcohol or drugs such that they are not able to engage in the intervention on more than one scheduled session.

2. If, in consultation with the participant's healthcare providers, there is concern for his/her safety and well-being (e.g., escalation of symptoms).

The participant could be withdrawn from study if, in consultation with the participant's health care providers, there is sufficient concern for his/her safety and well-being that the

participant may be withdrawn and re-directed to more appropriate care. This is described to the participant in the consent process.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

Statistical Hypotheses:

This project has one primary objective with a primary and a secondary hypothesis, and three secondary objectives with a single hypothesis as specified below.

Design Overview: A two-group (n = 165/165), randomized, repeated measures design will be employed. Three hundred thirty individuals with OUD engaged in MAT treatment will be recruited at one of three outpatient treatment sites, Harborview Medical Center, Country Doctor Community Health Centers, and North Olympic Healthcare Network. Enrolled patients will be individually randomized within sites to receive MABT+TAU (experimental group), or TAU only (control). An additional six sessions of MABT will be offered to those randomized to MABT who have continued substance use at six months. Assessments will be administered at baseline, post-intervention (3 months), and at 6, 9, and 12 month follow-up.

Primary Objective: Primary hypothesis: MABT+TAU will result in significantly fewer days of OU compared to TAU only from baseline to to 12 months.

The primary outcome is patient-reported days of illicit opioid use. Self-reported substance use is the recommended approach for intervention studies.[97] Days of illicit opioid use is defined as the number of days in which use of opioids other than MAT (buprenorphine or methadone) are reported. The TLFB method[3, 4] was determined for alcohol, amphetamines, cannabis, cocaine, hallucinogens, opiates, sedative-hypnotics, and any psychoactive substance for time periods of 0-30 days, 0-90 days, and 0-365 days, the correlations for all substances and for the three time periods ranged from .73 to .95, demonstrating test-retest reliability and validity.[98]

Primary Objective: Secondary hypothesis: MABT+TAU will result in significantly fewer days of non-opioid substance use compared to TAU only from baseline to baseline to 12 months.

Days of other illicit substance use is defined as the number of days of non-opioid substance use (.e.g. cocaine, methamphetamine, hallucinogens, non-prescribed benzodiazepines). We will also be reporting the number days the participant reports heavy drinking (>=5 drinks/day for males, and >=4 drinks per day for females).

Secondary Objective 1 Hypothesis: MABT+ TAU will result in significantly improved mental health (depression, anxiety, trauma), emotion regulation, interoceptive awareness and mindfulness skills), and physical health distress and pain (symptoms, pain severity, pain interference) compared to TAU only from baseline to 6 months (R33) and baseline to 12 months (R01).

Measures of mental health (distress symptoms and emotion regulation) will include three well-validated scales for diagnostic screening: the 9-item PHQ-9 to screen for depression[6, 7], the 7-item (α =.92) GAD-7 for anxiety[8], and the Posttraumatic Stress Disorder Checklist for *DSM-5* (PCL-5),[9] which assesses symptoms of post-traumatic stress on a Likert-type scale with 20 items (α =.94). The 4th measure, the Difficulty in Emotion Regulation Scale short form (DERS-SF)[10, 99] assesses difficulties in the modulation of emotional arousal. There are 18 items on a Likert-type scale (DERS α =.93; DERS short form α ranges from .78 to .91 with original DERS subscales) and four subscales that assess the degree of awareness, understanding, and acceptance of emotions, and the ability to act in desired ways regardless of the emotional state. The 5th & 6th measures, the Freiberg Mindfulness Questionnaire (FMQ) with 14 items[14], and the Multidimensional Assessment of Interoceptive Awareness (MAIA)[15] with 32 items on a Likert-type scale.

Physical symptoms will be assessed using the Medical Symptoms Checklist (MSC) and pain severity and interference using the Brief Pain Inventory (BPI). The MSC measures the frequency (0-8 scale) and severity (0-10 scale) of 29 common physical symptoms.[19] The BPI is a validated, widely used measurement tool for assessing clinical pain. In the U.S. it has been validated in non-cancer patients with pain[18] and HIV-infected patients.[100] The assessment includes 11 questions which provide information on pain severity and pain interference in the past week. Participants are initially asked if they have experienced any significant pain in the past week, and if they respond positively they answer subsequent questions about duration of pain, pain severity and interference. Pain severity is rated from 0 ("no pain") to 10 ("worst pain imaginable"), and participants are asked to rate their current pain as well as pain at its worst, at its best, and on average in the past week. Pain interference includes information on the impact of pain on general activity, walking, work, mood, enjoyment of life, relations with others, and sleep, asking the participant to rate interference on a scale from 0 ("does not interfere") to 10 ("completely interferes"), and is reported as the mean of seven questions. Participants who responded that they had no pain in the past week will be coded "0" for pain severity and interference. The BPI will be supplemented with a single question on duration of currently reported pain in order to establish whether the pain is acute or chronic.

Secondary Objective 2 Hypothesis: MABT + MAT will result in significantly reduced opioid craving, and significantly longer retention (days receiving medications), compared to TAU only from baseline to 6 months (R33) and baseline to 12 months (R01).

Opioid craving will be assessed using a single item numeric scale.[5] Participants are asked: "On a scale of 0–10, please indicate how much craving you have experienced during the past week," with responses anchored at "0=no craving at all" and "10-strongest craving ever". Retention will be defined as days retained in the program, or time to program discharge. Program discharges are documented in the electronic medical record (EMR) and date of discharge will be extracted from the record.

Secondary Objective 3 Hypothesis: Among participants in both groups who are using substances at 6 months, those in MABT group who receive additional MABT sessions (between 6-9 months) will show improved substance use at 12 months compared to those in TAU.

Exploration of the effectiveness of additional MABT dose offered at 6 months to those with continued substance use compared to those with continued substance use at 6 months in the TAU will be assessed using the Time-Line Follow-Back Interview (TLFB)[3, 4] self-reported as described in in the primary objective.

9.2 Sample Size and Randomization

Sample Size Calculation/Power Analysis:

Primary Objective The power for the primary aim of this study was determined for change in the days percent abstinent from opioids on the Timeline Followback Interview (TLFB) between the study's two arms (MABT +TAU, and TAU only) from baseline to 6 months (R33 aim) and baseline to 12 months (R01 aim). The power analysis was based on the prior MABT SUD R01 study (N=187), in which the proportion of abstinent days for MABT + TAU was 88.6 compared to 80.0 for TAU at 12 month follow-up.[90] Unlike the count data used to assess the number of days abstinent, proportional data is based on exact binomial confidence intervals and thus provides reliable and appropriate data to use for sample size calculation. The magnitude of effect in this prior R01 is expected to be similar for baseline to 6 month (R33) and baseline to 12-month effect for MABT + TAU vs. TAU (R01) in the current study.

A sample of 330, with an expected loss to follow-up of 20%, allows for .80 power to detect a minimum difference in proportion in days abstinent between MABT and TAU of .14, alpha =.05, two-tailed. Loss to follow-up is not expected to vary significantly due to treatment assignment. Since the actual analyses allow GEE models to analyze five time points (0, 3, 6, 9, 12 months) simultaneously for the R01 study, power will very likely be higher than these conservative estimates.

Secondary Outcomes For comparison of treatment arms on measures of secondary outcomes, we will have 80% power to detect a minimum difference of 0.4 SD. For comparison of medication-assisted treatment retention rates, we hypothesize that retention rates at 12 months will be 60% in the TAU arm and 77% in the MABT arm. The comparison of proportions will have power of 80% to detect this difference. Exploratory Aim: at 6 months after 20% attrition, we expect the total sample to be N = 264 (132 per group) and assume the ability to detect, at minimum, a 15% difference between MABT and TAU groups in proportion of abstinent days. Under these assumptions, the power at 12 months to detect a group difference comparing those using substances at 6 months (nonresponders) in control to those using substances (nonresponders) at 6 months in MABT groups (who have been offered additional sessions) is .65 for a 40% non-responder rate (n = 53 per group). While underpowered, this exploratory aim would provide a reasonable sample size to estimate power for future related research questions and allows us to look at the question of MABT dose and re-engagement for those needing additional treatment support within the primary analysis.

Missing Data: We will evaluate differences in baseline characteristics between participants lost to follow-up versus those who are not. Missing data patterns will also be evaluated including the frequency and percentage of those missing for each variable and the distribution of the number of variables missing. In addition, data collected to the point of lost to follow-up will be compared to the data of those who complete the study to examine possible missing data mechanisms, e.g., missing completely at random (MCAR), missing at random (MAR), or not missing at random (NMAR). Sensitivity analyses will be performed to assess the possible impact of the missing data on the study results. We will consider various methods for missing TLFB including multiple imputation and pattern mixture models.[105] Similar methods will be used for other drug use and opioid craving. We anticipate there should be no missing data for retention since patients who are lost to follow-up are discharged from the program, therefore "missingness" is part of the variable definition.

Randomization: Randomization will be provided by the project statistician. Stratified randomization, by study site, baseline self-reported chronic pain, and gender, will be used to distribute participants evenly between the two treatment conditions at each facility and within each gender. Randomization will use a modified minimization method algorithm[96] based on an overall imbalance score which measures how far out of balance (within strata) the study is for a given set of random assignments to ensure approximately equal accrual into the two experimental arms and to facilitate concealment of treatment assignments.

Treatment Assignment Procedures

Research coordinators will use the randomization program developed by the project statistician to determine the treatment assignment group following baseline data collection. Participants will be informed of their assignment within one week of the initial appointment by the Research Coordinator. Prior MABT studies showed no loss due to randomization to treatment group, thus we do not expect randomization to precipitate significant attrition. The Research Coordinator at each facility will not be blind to condition and will inform participants of their treatment condition and MABT therapist.

9.3 Definition of Populations

Intent-to-treat and dose analyses will be used. Intent to treat analyses includes all participants enrolled in the study. The dose analyses will examine TAU vs. MABT participants who completed > 75% of the initial intervention. Exploratory dose analyses will assess the impact of additional MABT sessions in the subpopulation of MABT-assigned participants who report using substances at the 6 month assessment.

9.4 Interim Analyses and Stopping Rules

No interim efficacy or futility analyses are planned because of the minimal risk level of the study and because patient outcomes are very unlikely to be worse in the intervention group in the study.

This study will be stopped prior to its completion only after discussion with and input from NCCIH if: (1) the intervention is associated with severe adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly

impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

Pertaining to the likelihood of adverse events, prior studies employing MABT to individuals with mental health concerns including two NIH-funded studies for individuals with substance use disorder, many of whom had moderate-severe depression and/or anxiety symptoms, and three additional studies for women with sexual trauma, have not identified significant risks associated with this intervention. However, should adverse events occur that are determined to be related to study participation, the MPIs and independent monitor (IM) will consult with both the UW IRB and the NICCH Program Officer about the likelihood of continued risk to study participants and will make a decision about whether it is necessary to stop the trial.

Should accrual monitoring demonstrate the need, the MPIs will consult with the data analyst and the IM to assess the impact of significant data loss due to problems in recruitment, retention, or data collection. Factors external to the study when interpreting the data, such as scientific developments or the new availability of proven clinical services that could have an impact on the safety of the participants, the performance of the study or the ethics of the study, will be reviewed by the MPIs annually.

9.5 Outcomes

9.5.1 Primary Outcome

The primary outcome is patient-reported days of abstinence from illicit opioid use measured at the 6 month endpoint for the R33 and 12month endpoint for the R01. Self-reported substance use is the recommended approach for intervention studies.[97] Days of illicit opioid use is defined as the number of days in which opioids other than MAT (buprenorphine or methadone) are used. Time-Line Follow-Back Interview (TLFB)[3, 4] will be used to assess opioid use, other illicit drugs, marijuana, and alcohol use. Participants will be asked first to identify what substances were used in the previous 90 days at each time assessment point (scheduled every 90 days). The participant will then be asked to use a calendar to retrospectively estimate their substance use, for each of the identified substances. Days of other illicit substance use is defined as the number of days (e.g. cocaine, methamphetamine, hallucinogens, or non-prescribed benzodiazepine) are reported using the TLFB.

9.5.2 Secondary Outcomes

Measures of mental health (distress symptoms and emotional well-being) will include three well-validated scales for diagnostic screening: the 9-item PHQ-9 to screen for depression[6, 7], the 7-item (α =.92) GAD-7 for anxiety[8], and the Posttraumatic Stress Disorder Checklist for *DSM-5* (PCL-5),[9] which assesses symptoms of post-traumatic stress on a Likert-type scale with 20 items (α =.94). The 4th measure, the Difficulty in Emotion Regulation Scale short form (DERS-SF)[10, 99] assesses difficulties in the modulation of emotional arousal. There are 18 items on a Likert-type scale (DERS α =.93; DERS short form α ranges from .78 to .91 with original DERS subscales) and four subscales that assess the degree of awareness, understanding, and acceptance of emotions, and the ability to act in desired ways regardless

of the emotional state. The 5th and 6th measures, the Freiberg Mindfulness Questionnaire (FMQ) with 14 items[14], and the Multidimensional Assessment of Interoceptive Awareness (MAIA)[15] with 32 items on a Likert-type scale are used to assess skills learned in the intervention.

Opioid craving will be assessed using a single item numeric scale.[5] Participants are asked: "On a scale of 0–10, please indicate how much craving you have experienced during the past week," with responses anchored at "0=no craving at all" and "10-strongest craving ever". Retention will be defined as days retained in the program, or time to program discharge. Program discharges are documented in the electronic medical record (EMR) and date of discharge will be extracted from the record.

Physical symptoms will be assessed using the Medical Symptoms Checklist (MSC) and pain severity and interference using the Brief Pain Inventory (BPI). The MSC measures the frequency (0-8 scale) and severity (0-10 scale) of 29 common physical symptoms.[19] The BPI is a validated, widely used measurement tool for assessing clinical pain. In the U.S. it has been validated in non-cancer patients with pain[18] and HIV-infected patients.[100] The assessment includes 11 questions which provide information on pain severity and pain interference in the past week. Participants are initially asked if they have experienced any significant pain in the past week, and if they respond positively they answer subsequent questions about duration of pain, pain severity and interference. Pain severity is rated from 0 ("no pain") to 10 ("worst pain imaginable"), and participants are asked to rate their current pain as well as pain at its worst, at its best, and on average in the past week. Pain interference includes information on the impact of pain on general activity, walking, work, mood, enjoyment of life, relations with others, and sleep, asking the participant to rate interference on a scale from 0 ("does not interfere") to 10 ("completely interferes"), and is reported as the mean of seven questions. Participants who responded that they had no pain in the past week will be coded "0" for pain severity and interference. The BPI will be supplemented with a single question on duration of currently reported pain in order to establish whether the pain is acute or chronic.

Table 1: Outcomes Measurement Schedule

Concept	Measure	Assessment Time-Point (from baseline)				
		Baseline	12 weeks	24 weeks	39 weeks	52 weeks
Baseline and Descriptive Information						
Demographic/Health History	Health History Form[1],(EHR)	X				
Trauma history	TLEQ[2]	X				
Economic Indicators	Employment, Health Utilization, Legal Status	X	X	X	X	X
Substance Use						
Substance use	TLFB Interview[3, 4] Urine Toxicology Opioid Craving [5] Treatment Retention (EHR)	X X X	X X X	X X X X	X X X	X X X X
Mental Health Distress, Emotional Well-being, Physical Health Distress and Pain						

Distress (Depression, Anxiety PTSD Symptoms)	PHQ-9[6, 7] GAD-7[8] PCL-5[9]	X X X	X X X	X X X	X X X	X X X
Emotion Regulation Difficulties	DERS-SF[10]	X	X	X	X	X
Mindfulness and Interoceptive Awareness Skills	FMQ [14] MAIA [15]	X X	X X	X X	X X	X X
Co-morbid Pain and Interference	BPI[18]	X	X	X	X	X
Physical Symptoms	MSC [19]	X	X	X	X	X
Intervention Satisfaction						
Treatment satisfaction and perceived skills*	MABT Follow-up Questionnaire		X		X	

* MABT group only; NA = not applicable; EHR = Electronic Health Records.

9.6 Data Analyses

Primary Analysis To test the primary hypotheses, generalized linear regression models for dependent data will be used to compare percent days abstinent from opioid use in the two study groups between baseline to 6 months for the R33 study aims, and baseline to 12 months for the R01 study aims. Sensitivity analyses will also explore modeling opioid use as percent days abstinent during the assessment periods using Generalized Estimating Equations (GEE) [106] with a logit link and an exchangeable correlation structure. We will fit difference within group correlations structures (unstructured, independent, exchangeable, autoregressive) seeking the correlation structure that combines the fewest parameters with the best measure of fit using Akaike information criterion (AIC) and Bayesian information criterion (BIC). The logarithm of the total number of days in the assessment period will be included as an offset variable to account for the time at risk of relapse. The same analysis will be done to examine percent days abstinent on other illicit drugs and alcohol.

Secondary Analyses Analyses of secondary outcomes (mental and physical health outcomes and opioid craving) will utilize GEE as described above. Longitudinal analyses will examine treatment by time interactions on each of the outcomes. Analyses of retention in medication-assisted treatment will be done using a test of proportions retained in MAT as well as the log-rank test to compare survival curves. A sensitivity analysis will use Cox regression to adjust for pre-treatment covariates. Last, we plan to include exploratory analyses to also examine treatment by gender interactions.

Exploratory Analysis Linear regression model using GEE will be used to explore the effect of additional MABT dose on days abstinent from opioid use and related health outcomes at 12 months among the MABT 6 month non-responders compared to control non-responders. Characteristics of responders will be compared to those of non-responders using t-tests, chi-square, or Fisher's exact tests.

In addition, we will explore the relationship with dose, within the MABT group. Dose response functions will be estimated thorough a regression approach treating the number of sessions as the continuous treatment variable. Such models are appropriate when the treatment intensity is endogenous (that is, selection into treatment depends on both observable and unobservable factors).

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Data collection will follow study procedures as specified in standard operating procedures developed from the research protocol. The MPIs will work with the data manager and project manager to design forms and a database that maximizes accurate data entry by setting appropriate ranges and expected data types (e.g., text, date, etc.). The project manager will ensure the proper procedural trainings occur for the research coordinators and interventionists on the data collection procedures and forms, including adherence to procedures to protect participant confidentiality (see Section 11.3).

10.2 Data Management

Clinical Sites

The research coordinators (RC) will collect data from participants and the interventionists at the clinical sites. Using a laptop computer with password and network protections, RCs will enter demographic information, screening results, tracking data, primary outcome (TLFB) data, urine toxicology results, and EHR-derived retention data directly into the secure study databases. During assessment visits, RCs will open the survey instruments via REDcap on the laptop (in a guest-only UW account) and allow participants to complete the measures independently (unless he/she requires assistance due to low/no literacy, for which the RC will read and record survey information). Paper consent files will be stored in a locked filing cabinet separately from paper files (e.g., TLFB calendar worksheet, handwritten process evaluations) associated with the participant's study ID number.

Interventionists will provide the RC with process evaluations and session audio files, which the RC will upload to the secure server. Interventionists will also provide the RC with AE/SAE related forms if reported during the session.

Data Management Center

The data manager, project manager, and MPIs will be responsible for creating and maintaining the study databases. Survey measure data will be collected and stored in REDcap. Tracking data and non-survey outcomes data entered by the RCs at the clinical sites will be stored in REDcap, Access, or Excel and monitored as described in section 10.3.5 below.

Data Collection Forms

Data collections forms are mostly electronic using primarily radio buttons to complete Likert-type scales. A paper calendar is used to elicit illicit drug use recall in the TLFB procedures and to calculate totals, and the results entered into the REDCap database along with urinalysis results. Paper forms will be used to record process evaluations and events (e.g., AE/SAE, UP, PD), then submitted to the RC to be scanned and uploaded to the secure shared server folder or for electronic input into the study database.

10.3 Quality Assurance

10.3.1 Training

The research coordinators will be directly overseen by the project manager and the MPIs. Coordinators will undergo training including reading and review of the Standard Operating Procedures of the study and skills review of accessing and entering data. Meetings every two weeks between the project manager and RCs, and monthly including Dr. Price, will provide RCs opportunity to discuss issues that arise; however, they will be encouraged to reach out at any time with questions or concerns regardless of scheduled meetings.

The MABT interventionists will be licensed to practice in Washington State, as massage therapists (LMT) or mental health counselors (licensed clinical social workers or mental health counselors). They will have clinical experience working with individuals in SUD treatment and an educational background in mental health (graduate degree or certificate training), and a minimum of 5 years in clinical practice. The interventionists will be trained to the MABT protocol by Dr. Price.

To track treatment fidelity, the research interventionists will complete a process evaluation form that includes a fidelity checklist (an integral part of the MABT training manual and protocol) at the completion of each intervention session. In addition, all intervention sessions will be audio-recorded to monitor compliance to the research protocols and to facilitate ongoing clinical supervision. Ms. Wiechman, a trained MABT therapist and instructor who has worked on multiple prior MABT research studies with Dr. Price, will supervise the MABT interventionists. Supervision will include ongoing review of audiotaped sessions and process evaluation forms and regular feedback to interventionists based on this review.

10.3.2 Quality Control Committee

There is no quality control committee. Data quality and protocol adherence will be monitored by the study team.

10.3.3 Metrics

Data collected via REDCap surveys/databases allow set ranges and the inability to select multiple responses thus ensuring that a single and valid response for each item is collected. Distribution properties, scale means and variances for all outcome measures will be scrutinized. We will conduct measurement studies with data from this study, performing validity (correlations, CFA) and traditional reliability analyses (Cronbach's α) for all measures.

10.3.4 Protocol Deviations

Protocol deviations will be captured by review of data and related procedures on a regular basis by the Project Manager (supervising RC) and PI providing supervision of interventionists (Dr. Price). These deviations will be recorded and saved on the protected study database, and reviewed with the larger team at the regularly scheduled team meetings, or sooner if repeated errors are found.

10.3.5 Monitoring

Results of data checks (including those in table 4) and for outcomes as described in 10.3.3 will be shared with the MPIs at quarterly team meetings, or sooner if repeated errors are found. Compliance will be addressed by quarterly audits/monitoring of study-related materials (e.g., consent forms, source documents, adverse event logs, etc.).

Table 4. Data Monitoring

Data Type	Frequency of Review	Reviewer
Subject accrual (including compliance with protocol enrollment criteria) and meeting milestones	Every 2 weeks Monthly Quarterly	Project Manager MPIs Independent Monitor (by report)
Status of all enrolled subjects, as of date of reporting	Monthly Quarterly	Project Manager MPIs Independent Monitor (by report)
Adherence data regarding study visits and intervention	Monthly Quarterly	Project Manager MPIs, Independent Monitor (by report)
AEs and rates	Weekly Quarterly	Project Manager, MPIs Independent Monitor (by report)
Unanticipated, serious, possibly related SAEs	Per occurrence	MPIs, Independent Monitor, NCCIH
Reportable New Information (e.g., unanticipated problem, serious non-compliance)	Per occurrence	MPIs, UW IRB, Independent Monitor

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

We will receive approval from the University of Washington Institutional Review Board before commencing the study with human subjects, and will adhere to its policies regarding subsequent modifications to the approved application.

11.2 Informed Consent Forms

Verbal informed consent will be obtained prior to initiating screening procedures. A signed consent form will be obtained from each participant. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant or legal guardian and this fact will be documented in the participant's record. Individuals who cannot provide informed consent will be excluded, such as in the scenario of acute intoxication, overt psychosis or cognitive

impairment, as well as participants who do not speak or read English. An adapted 7-item Mini-Mental Status Exam, with a cut-off score indicating ineligibility, will be applied if there is questionable difficulty comprehending the informed consent and to assess cognitive impairment.

11.3 Participant Confidentiality

The structures to assure confidentiality include the following: each enrolled participant will receive a unique identification number; research data collection and data entry forms will be identified only with this number. Only the master enrollment list, written informed consent forms, and participant locator information will have identifying information on them. These documents will be kept on a secure network or in a locked file cabinet in the PI and project manager's offices. Computer systems will be password protected, and accessible only to research staff needing the information for follow-up and monitoring purposes. Files stored on UW servers will be protected by electronic 'firewalls' that restrict access to designated users. The data manager will receive only coded information entered into the database under study ID numbers. Any data, forms, reports, recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. No study information will be released without written permission of the participant, except as necessary for monitoring by IRB, NCCIH, and the OHRP. We also will preserve confidentiality during adverse event reporting, by not including any identifying information unless invoking the UW Human Subjects Assistance Program at the request of an eligible study participant.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCCIH, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12. COMMITTEES

Not applicable.

13. PUBLICATION OF RESEARCH FINDINGS

Research findings will be disseminated through presentations, abstract submissions, and manuscripts with appropriate acknowledgement and disclaimer of NCCIH. Dissemination efforts also include sharing of best practices across SAMHSA networks, allowing a platform for widespread implementation of successful strategies, which can facilitate the adoption of MABT to improve MAT and related health outcomes, a key goal of the WA-STR project. For example, integration of this trial within programs funded through the Washington State STR Hub & Spoke Project allows for future expansion of the intervention should trial data show improved treatment outcomes. Each of the six Hub & Spoke networks funded through STR plan to incorporate elements of the Nurse Care Manager model in a variety of primary care, behavioral health and substance use disorder treatment programs with connections to key

community sites, including needle and syringe exchange programs, hospitals, correctional facilities, and drug courts. In addition, real world evidence of MABT effectiveness within WA-STR would be an important step towards establishing it as qualifying for inclusion within SAMHSA's National Registry of Evidence-Based Programs and Practices.

14. REFERENCES

1. McLellan, A.T., et al., *The Fifth Edition of the Addiction Severity Index*. J Subst Abuse Treat, 1992. **9**(3): p. 199-213.
2. Kubany, E.S., et al., *Development and preliminary validation of a brief broad-spectrum measure of trauma exposure: the Traumatic Life Events Questionnaire*. Psychol Assess, 2000. **12**(2): p. 210-24.
3. Sobell, L. and M. Sobell, *Alcohol Timeline Followback User's Manual*. 1995, Toronto: Addiction Research Foundation.
4. Sobell, L., et al., *The reliability of the Timeline Followback method applied to drug, cigarette, and cannabis use*, in *The 30th Annual Meeting of the Association for Advancement of Behavior Therapy*. 1996: New York.
5. Rosenberg, H., *Clinical and laboratory assessment of the subjective experience of drug craving*. Clin Psychol Rev, 2009. **29**(6): p. 519-34.
6. Kroenke, K., R.L. Spitzer, and J.B. Williams, *The PHQ-9: validity of a brief depression severity measure*. J Gen Intern Med, 2001. **16**(9): p. 606-13.
7. Kroenke, K., et al., *The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review*. Gen Hosp Psychiatry, 2010. **32**(4): p. 345-59.
8. Spitzer, R.L., et al., *A brief measure for assessing generalized anxiety disorder: the GAD-7*. Arch Intern Med, 2006. **166**(10): p. 1092-7.
9. Dickstein, B.D., et al., *Diagnostic Utility of the Posttraumatic Stress Disorder (PTSD) Checklist for Identifying Full and Partial PTSD in Active-Duty Military*. Assessment, 2015. **22**(3): p. 289-297.
10. Kaufman, E., et al., *The difficulties in emotion regulation scale short form (DERS-SF): Validation and replication in adolescent and adult samples*. Journal of Psychopathology and Behavioral Assessment, 2016. **38**(3): p. 443-455.
11. Diener, E., et al., *New well-being measures: short scales to assess flourishing and positive and negative feelings*. Social Indicators Research, 2010. **97**: p. 143-156.
12. Keyes, C.L., *Promoting and protecting mental health as flourishing: a complementary strategy for improving national mental health*. Am Psychol, 2007. **62**(2): p. 95-108.
13. Smith, B.W., et al., *The brief resilience scale: assessing the ability to bounce back*. Int J Behav Med, 2008. **15**(3): p. 194-200.
14. Walach, H., et al., *Measuring mindfulness - the Freiburg Mindfulness Inventory (FMI)*. Personality and Individual Differences, 2006. **40**(8): p. 1543-1555.
15. Mehling, W., et al., *Multidimensional Assessment of Interoceptive Awareness (MAIA)*. PLoS ONE, 2012. **7**(11): p. e48230
16. Bagby, R.M., G.J. Taylor, and J.D. Parker, *The Twenty-item Toronto Alexithymia Scale--II. Convergent, discriminant, and concurrent validity*. J Psychosom Res, 1994. **38**(1): p. 33-40.
17. Parker, J.D., G.J. Taylor, and R.M. Bagby, *The 20-Item Toronto Alexithymia Scale. III. Reliability and factorial validity in a community population*. J Psychosom Res, 2003. **55**(3): p. 269-75.

18. Keller, S., et al., *Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain.* Clin J Pain, 2004. **20**(5): p. 309-18.
19. Leserman, J., et al., *Selected symptoms associated with sexual and physical abuse history among female patients with gastrointestinal disorders: the impact on subsequent health care visits.* Psychol Med, 1998. **28**(2): p. 417-25.
20. SAMHSA, *SAMHSA to award nearly $1 billion in new grants to address the nation's opioid crisis.* 2016.
21. Fullerton, C.A., et al., *Medication-assisted treatment with methadone: assessing the evidence.* Psychiatr Serv, 2014. **65**(2): p. 146-57.
22. Saxon, A.J., et al., *Medication-assisted treatment for opioid addiction: methadone and buprenorphine.* J Food Drug Anal, 2013. **21**(4): p. S69-s72.
23. Mattick, R.P., et al., *Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence.* Cochrane Database Syst Rev, 2014(2): p. CD002207.
24. Gowing, L., et al., *Substitution treatment of injecting opioid users for prevention of HIV infection.* Cochrane Database Syst Rev, 2008(2): p. Cd004145.
25. MacArthur, G.J., et al., *Opiate substitution treatment and HIV transmission in people who inject drugs: systematic review and meta-analysis.* Bmj, 2012. **345**: p. e5945.
26. Tsui, J.I., et al., *Association of opioid agonist therapy with lower incidence of hepatitis C virus infection in young adult injection drug users.* JAMA Intern Med, 2014. **174**(12): p. 1974-81.
27. Nolan, S., et al., *The impact of methadone maintenance therapy on hepatitis C incidence among illicit drug users.* Addiction, 2014. **109**(12): p. 2053-9.
28. White, B., et al., *Opioid substitution therapy protects against hepatitis C virus acquisition in people who inject drugs: the HITS-c study.* Med J Aust, 2014. **201**(6): p. 326-9.
29. Schwartz, R.P., et al., *Opioid agonist treatments and heroin overdose deaths in Baltimore, Maryland, 1995-2009.* Am J Public Health, 2013. **103**(5): p. 917-22.
30. Hser, Y.I., et al., *Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial.* Addiction, 2014. **109**(1): p. 79-87.
31. Weinstein, Z.M., et al., *Long-term retention in Office Based Opioid Treatment with buprenorphine.* J Subst Abuse Treat, 2017. **74**: p. 65-70.
32. Bhatraju, E.P., et al., *Public sector low threshold office-based buprenorphine treatment: outcomes at year 7.* Addict Sci Clin Pract, 2017. **12**(1): p. 7.
33. Soeffing, J.M., et al., *Buprenorphine maintenance treatment in a primary care setting: outcomes at 1 year.* J Subst Abuse Treat, 2009. **37**(4): p. 426-30.
34. Alford, D.P., et al., *Collaborative care of opioid-addicted patients in primary care using buprenorphine: five-year experience.* Arch Intern Med, 2011. **171**(5): p. 425-31.
35. Burns, L., et al., *A longitudinal comparison of retention in buprenorphine and methadone treatment for opioid dependence in New South Wales, Australia.* Addiction, 2015. **110**(4): p. 646-55.
36. Schwarz, R., et al., *Retention on buprenorphine treatment reduces emergency department utilization, but not hospitalization, among treatment-seeking patients with opioid dependence.* J Subst Abuse Treat, 2012. **43**(4): p. 451-7.
37. Treatment., C.f.S.A., *Medication-assisted treatment for opioid addiction in opioid treatment programs,Treatment Improvement Protocol (TIP) Series 43.* 2006, Substance Abuse and Mental Health Services Administration: Rockville, MD.

38. Kidorf M, D.E., King VL, Neufeld K, Beilenson PL, Brooner RK, *Prevalence of psychiatric and substance use disorders in opioid abusers in a community syringe exchange program.* Drug Alcohol Depend, 2004. **74**: p. 115-122.
39. Senbanjo, R., K. Wolff, and J. Marshall, *Excessive alcohol consumption is associated with reduced quality of life among methadone patients.* Addiction, 2007. **102**(2): p. 257-63.
40. Stenbacka, M., et al., *Problem drinking in relation to treatment outcome among opiate addicts in methadone maintenance treatment.* Drug Alcohol Rev, 2004. **26**: p. 55-63.
41. Barry, D.T., et al., *Relations Among Psychopathology, Substance Use, and Physical Pain Experiences in Methadone-Maintained Patients.* Journal of Clinical Psychiatry, 2009. **70**(9): p. 1213-1218.
42. Carpentier, P.J., et al., *Psychiatric comorbidity reduces quality of life in chronic methadone maintained patients.* Am J Addict, 2009. **18**(6): p. 470-80.
43. Ross, J., et al., *The characteristics of heroin users entering treatment: findings from the Australian treatment outcome study (ATOS).* Drug Alcohol Rev, 2005. **24**(5): p. 411-8.
44. Ilgen, M.A., J.A. Trafton, and K. Humphreys, *Response to methadone maintenance treatment of opiate dependent patients with and without significant pain.* Drug Alcohol Depend, 2006. **82**(3): p. 187-93.
45. Trafton, J.A., et al., *Treatment needs associated with pain in substance use disorder patients: implications for concurrent treatment.* Drug Alcohol Depend, 2004. **73**(1): p. 23-31.
46. Ouimette, P., J. Read, and P.J. Brown, *Consistency of retrospective reports of DSM-IV criterion A traumatic stressors among substance use disorder patients.* J Trauma Stress, 2005. **18**(1): p. 43-51.
47. Cottler, L.B., et al., *Posttraumatic stress disorder among substance users from the general population.* Am J Psychiatry, 1992. **149**(5): p. 664-70.
48. Mills, K.L., et al., *Trauma, PTSD, and substance use disorders: findings from the Australian National Survey of Mental Health and Well-Being.* Am J Psychiatry, 2006. **163**(4): p. 652-8.
49. Fiellin, D.A., et al., *Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence.* N Engl J Med, 2006. **355**(4): p. 365-74.
50. Weiss, R.D., et al., *Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial.* Arch Gen Psychiatry, 2011. **68**(12): p. 1238-46.
51. Kamal, F., et al., *Factors affecting the outcome of methadone maintenance treatment in opiate dependence.* Ir Med J, 2007. **100**(3): p. 393-7.
52. Kreek, M.J., et al., *Pharmacotherapy in the treatment of addiction: methadone.* J Addict Dis, 2010. **29**(2): p. 200-16.
53. Simpson, D.D., G.W. Joe, and G.A. Rowan-Szal, *Drug abuse treatment retention and process effects on follow-up outcomes.* Drug Alcohol Depend, 1997. **47**(3): p. 227-35.
54. Millson, P.E., et al., *Self-perceived health among Canadian opiate users: a comparison to the general population and to other chronic disease populations.* Can J Public Health, 2004. **95**(2): p. 99-103.
55. Rosenblum, A., et al., *Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities.* JAMA, 2003. **289**(18): p. 2370-8.
56. Potter, J.S., S.J. Shiffman, and R.D. Weiss, *Chronic pain severity in opioid-dependent patients.* Am J Drug Alcohol Abuse, 2008. **34**(1): p. 101-7.

57. Back, S.E., et al., *Comparative profiles of men and women with opioid dependence: results from a national multisite effectiveness trial*. Am J Drug Alcohol Abuse, 2011. **37**(5): p. 313-23.
58. Barry, D.T., et al., *Exploring Relations Among Traumatic, Posttraumatic, and Physical Pain Experiences in Methadone-Maintained Patients*. J Pain, 2011.
59. Clark, M.R., K.B. Stoller, and R.K. Brooner, *Assessment and management of chronic pain in individuals seeking treatment for opioid dependence disorder*. Can J Psychiatry, 2008. **53**(8): p. 496-508.
60. Dehghani-Arani, F., R. Rostami, and H. Nadali, *Neurofeedback training for opiate addiction: improvement of mental health and craving*. Appl Psychophysiol Biofeedback, 2013. **38**(2): p. 133-41.
61. Manheimer, E., B.J. Anderson, and M.D. Stein, *Use and assessment of complementary and alternative therapies by intravenous drug users*. Am J Drug Alcohol Abuse, 2003. **29**(2): p. 401-13.
62. Barry, D.T., et al., *Allopathic, complementary, and alternative medical treatment utilization for pain among methadone-maintained patients*. Am J Addict, 2009. **18**(5): p. 379-85.
63. Wachholtz, A., D. Ziedonis, and G. Gonzalez, *Comorbid pain and opioid addiction: psychosocial and pharmacological treatments*. Subst Use Misuse, 2011. **46**(12): p. 1536-52.
64. Cherkin, D.C., et al., *Effect of Mindfulness-Based Stress Reduction vs Cognitive Behavioral Therapy or Usual Care on Back Pain and Functional Limitations in Adults With Chronic Low Back Pain: A Randomized Clinical Trial*. JAMA, 2016. **315**(12): p. 1240-9.
65. Morone, N.E., et al., *A Mind-Body Program for Older Adults With Chronic Low Back Pain: A Randomized Clinical Trial*. JAMA Intern Med, 2016. **176**(3): p. 329-37.
66. Garland, E.L., et al., *Mindfulness-oriented recovery enhancement for chronic pain and prescription opioid misuse: results from an early-stage randomized controlled trial*. J Consult Clin Psychol, 2014. **82**(3): p. 448-59.
67. Craig, A.D., *Interoception: the sense of the physiological condition of the body*. Curr Opin Neurobiol, 2003. **13**(4): p. 500-5.
68. Cameron, O.G., *Interoception: the inside story--a model for psychosomatic processes*. Psychosom Med, 2001. **63**(5): p. 697-710.
69. Naqvi, N.H. and A. Bechara, *The insula and drug addiction: an interoceptive view of pleasure, urges, and decision-making*. Brain Struct Funct, 2010. **214**(5-6): p. 435-50.
70. Paulus, M.P., S.F. Tapert, and G. Schulteis, *The role of interoception and alliesthesia in addiction*. Pharmacol Biochem Behav, 2009. **94**(1): p. 1-7.
71. Paulus, M.P. and J.L. Stewart, *Interoception and drug addiction*. Neuropharmacology, 2014. **76 Pt B**: p. 342-50.
72. Goldstein, R., et al., *The Neurocircuity of Impaired Insight*. Trends in Cognitive Sciences, 2010. **13**(9): p. 372-378.
73. Verdejo-Garcia, A., L. Clark, and B.D. Dunn, *The role of interoception in addiction: a critical review*. Neurosci Biobehav Rev, 2012. **36**(8): p. 1857-69.
74. Noel, X., D. Brevers, and A. Bechara, *A neurocognitive approach to understanding the neurobiology of addiction*. Curr Opin Neurobiol, 2013. **23**(4): p. 632-8.
75. Sinha, R. and C.S. Li, *Imaging stress- and cue-induced drug and alcohol craving: association with relapse and clinical implications*. Drug Alcohol Rev, 2007. **26**(1): p. 25-31.

76. Gowin, J.L., et al., *Attenuated Insular Processing During Risk Predicts Relapse in Early Abstinent Methamphetamine-Dependent Individuals*. Neuropsychopharmacology, 2014. **39**(6): p. 1379-1387.
77. Stewart, J.L., et al., *Do you feel alright? Attenuated neural processing of aversive interoceptive stimuli in current stimulant users*. Psychophysiology, 2015. **52**(2): p. 249-62.
78. Farb, N.A., et al., *Interoception, Contemplative Practice and Health*. Frontiers in Psychology, 2015. **6**: p. e763.
79. Wu, L.T. and D.G. Blazer, *Substance use disorders and psychiatric comorbidity in mid and later life: a review*. International Journal of Epidemiology, 2014. **43**(2): p. 304-317.
80. Schmidt, A.J., R.E. Gierlings, and M.L. Peters, *Environmental and interoceptive influences on chronic low back pain behavior*. Pain, 1989. **38**(2): p. 137-43.
81. Wald, J. and S. Taylor, *Responses to interoceptive exposure in people with posttraumatic stress disorder (PTSD): a preliminary analysis of induced anxiety reactions and trauma memories and their relationship to anxiety sensitivity and PTSD symptom severity*. Cogn Behav Ther, 2008. **37**(2): p. 90-100.
82. Sinha, R., et al., *Enhanced Negative Emotion and Alcohol Craving, and Altered Physiological Responses Following Stress and Cue Exposure in Alcohol Dependent Individuals*. Neuropsychopharmacology, 2009. **34**(5): p. 1198-1208.
83. Price, C.J., *Body-oriented therapy in recovery from child sexual abuse: an efficacy study*. Altern Ther Health Med, 2005. **11**(5): p. 46-57.
84. Price, C.J., *Dissociation reduction in body therapy during sexual abuse recovery*. Complement Ther Clin Pract, 2007. **13**(2): p. 116-28.
85. Price, C.J., et al., *Mindful awareness in body-oriented therapy as an adjunct to women's substance use disorder treatment: a pilot feasibility study*. J Subst Abuse Treat, 2012. **43**(1): p. 94-107.
86. Price, C.J., et al., *Mindful awareness in body-oriented therapy for female veterans with post-traumatic stress disorder taking prescription analgesics for chronic pain: a feasibility study*. Altern Ther Health Med, 2007. **13**(6): p. 32-40.
87. Rounsaville, B.J., K.M. Carroll, and L.S. Onken, *A Stage Model of Behavioral Therapies research: Getting started and moving on from stage I*. Clinical Psychology-Science and Practice, 2001. **8**(2): p. 133-142.
88. Price, C.J., et al., *Implementation and Acceptability of Mindful Awareness in Body-oriented Therapy in Women's Substance Use Disorder Treatment*. Journal of Alternative and Complementary Medicine, 2012. **18**(5): p. 1-9.
89. Price, C.J., et al., *Immediate Effects of Interoceptive Awareness Training through Mindful Awareness in Body-oriented Therapy (MABT) for Women in Substance Use Disorder Treatment*. Subst Abus, 2018: p. 1-44.
90. Price, C.J., et al., *Longitudinal effects of interoceptive awareness training through mindful awareness in body-oriented therapy (MABT) as an adjunct to women's substance use disorder treatment: A randomized controlled trial*. Drug Alcohol Depend, 2019. **198**: p. 140-149.
91. Tsui, J.I., et al., *Hepatitis C virus infection and pain sensitivity in patients on methadone or buprenorphine maintenance therapy for opioid use disorders*. Drug Alcohol Depend, 2015. **153**: p. 286-92.
92. Tsui, J.I., et al., *Chronic pain, craving, and illicit opioid use among patients receiving opioid agonist therapy*. Drug Alcohol Depend, 2016. **166**: p. 26-31.
93. Price, C., *Body-Oriented Therapy in Sexual Abuse Recovery: A Pilot-Test Comparison*. Journal of Bodywork and Movement Therapies, 2006. **10**: p. 58-64.

94. Price, C.J., et al., *Developing Compassionate Self-care Skills in Persons Living with HIV: a Pilot Study to Examine Mindful Awareness in Body-oriented Therapy Feasibility and Acceptability*. International journal of therapeutic massage & bodywork, 2013. **6**(2): p. 9-19.
95. Price, C., et al. *Interoceptive AwarenessTraining for Emotion Regulation Through Mindful Body Awareness Among Women in Treatment forSubstance Use Disorder*. in *International Research Congress on Integrative Medicine and Health*. 2016. Las Vegas, NV: Journal of Complementary and Alternative Medicine.
96. Pocock, S.J., *Clinical trials : a practical approach*. 1983, John Wiley & Sons,: Chichester, England. p. 1 online resource (280 p.
97. Donovan, D.M., et al., *Primary outcome indices in illicit drug dependence treatment research: systematic approach to selection and measurement of drug use end-points in clinical trials.* Addiction, 2011.
98. Fals-Stewart, W., et al., *The timeline followback reports of psychoactive substance use by drug-abusing patients: psychometric properties.* J Consult Clin Psychol, 2000. **68**(1): p. 134-44.
99. Gratz, K.L. and L. Roemer, *Multidimensional assessment of emotion regulation and dysregulation: Development, factor structure, and initial validation of the difficulties in emotion regulation scale*. Journal of Psychopathology and Behavioral Assessment, 2004. **26**(1): p. 41-54.
100. Breitbart, W., et al., *A comparison of pain report and adequacy of analgesic therapy in ambulatory AIDS patients with and without a history of substance abuse.* Pain, 1997. **72**(1-2): p. 235-43.
101. Speaker, E., et al., *Washington State Medication Assisted Treatment – Prescription Drug and Opioid Addiction Project: Year One Performance*. 2017, Washington State Department of Social and Health Services.
102. Folstein, M., S. Folstein, and P. McHugh, *Mini-Mental State: A practical method for grading the state of patients for the clinician.* Journal of Psychiatric Research, 1975. **12**: p. 189-198.
103. Baer, R.A., G.T. Smith, and K.B. Allen, *Assessment of mindfulness by self-report: the Kentucky inventory of mindfulness skills.* Assessment, 2004. **11**(3): p. 191-206.
104. Price, C., et al., *Perceived Helpfulness and Unfolding Processes in Body-oriented Therapy Practice*. The Indo-Pacific Journal of Phenomenology, 2011. **11**(2): p. 1-15.
105. Hedeker, D. and R.D. Gibbons, *Application of random-effects pattern-mixture models for missing data in longitudinal studies.* Psychological methods, 1997. **2**(1): p. 64.
106. Liang, K.Y. and S.L. Zeger, *Longitudinal Data-Analysis Using Generalized Linear-Models.* Biometrika, 1986. **73**(1): p. 13-22.