Official Title: Psychosocial pain management to improve opioid use disorder treatment outcomes: randomized controlled trial

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Psychosocial pain management to improve opioid use disorder treatment outcomes: A randomized controlled trial

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Under NCCIH Review

STATEMENT OF COMPLIANCE

This trial will be carried out in accordance with the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and GCP Training.

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

PROJECT FUNDING

Award 4R33AT010106-02 provides funding from the National Institute on Drug Abuse (NIDA) and the National Institute of Neurological Disorders and Stroke (NINDS).

Award 1R01AT010797-01 provides funding from the National Institute of Neurological Disorders and Stroke (NINDS).

Any papers published under the auspices of this award must cite the funding support of all institutes.

Each publication, press release or other documentation that cites results from NIH grant supported research must include an acknowledgement of NIH grant support and disclaimer such as, “This publication or project was made possible by Grant Number R33AT010106 from the National Center for Complementary and Integrative Health (NCCIH), the National Institute on Drug Abuse (NIDA) and the National Institute of Neurological Disorders and Stroke (NINDS). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NCCIH, NIDA, NINDS or the National Institutes of Health.”

Tool Revision History

Version Number: 0.1
Version Date: 06 June 2019
Summary of Revisions Made: Not applicable; this is the first version of the protocol

Version Number: 0.2
Version Date: 10 January 2020
Summary of Revisions Made: Entire protocol revised based on NCCIH review and project modification, initial IRBMED approved version

Version Number: 0.3
Version Date: 07 May 2020

Summary of Revisions Made: clarify aims including defining singular primary outcome, update IMC members, add recruitment sites, revise recruitment, consent and baseline procedures to allow for remote activities

Version Number: 0.4
Version Date: 30 October 2020
Summary of Revisions Made: add recruitment sites, revise recruitment, and minor grammatical errors

Version Number: 5.0
Version Date: 1 February 2021
Summary of Revisions Made: changes to eligibility, add national recruitment sites and expand recruitment strategies

Version Number: 6.0
Version Date: 24 July 2021
Summary of Revisions Made: changes to urine drug screening

Version Number: 7.0
Version Date: 01 October 2021
Summary of Revisions Made: revisions to assessment measures

Version Number: 8.0
Version Date: 12 January 2022
Summary of Revisions Made: Addition of recruitment site

Version Number: 9.0
Version Date: 27 July 2022
Summary of Revisions Made: Addition of website recruitment, update IMC member, clarification of VA IRB oversight

Version Number: 10.0
Version Date: 01 September 2022
Summary of Revisions Made: Removal of Co-Investigator Debra Pinals

Version Number: 11.0
Version Date: 03 November 2022
Summary of Revisions Made: Addition of exclusion criteria, clarify inclusion criteria and remote recruitment procedures

Version Number: 12.0
Version Date: 06 November 2023
Summary of Revisions Made: Update to Secondary Aim 4 recruitment information

Protocol Note

Per the request of the funding agency, this protocol has been written to include two NCCIH funded research projects – an R33 grant entitled "Psychosocial pain management to improve opioid use disorder treatment outcomes" (Parent grant; 4 R33 AT010106-02; PI: Ilgen) and an R01 grant entitled "Enhancing the impact of behavioral pain management on MAT outcomes" (1 R01 AT010797-01; Multiple PIs: Ilgen and Lin). Although there are two different funded grant numbers, both studies will be combined to achieve one collective set of project aims and outcomes, discussed within the protocol below. This study will have a working project title of **The Persist Study**.

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PRÉCIS

Psychosocial pain management to improve opioid use disorder treatment outcomes: A randomized controlled trial

With efforts to increase delivery of medication assisted treatment (MAT) to the large population of individuals with opioid use disorders (OUD), it is critical to also deliver effective interventions for chronic pain, which is both prevalent and often an underlying factor driving poor OUD treatment outcomes. Psychosocial interventions for pain management are a highly promising strategy for addressing chronic pain, but have not been tested in patients receiving MAT, specifically buprenorphine (the term we will use to refer to all buprenorphine products including buprenorphine/naloxone) for OUD. This study seeks to address this issue by conducting a randomized controlled trial of a psychosocial pain management intervention (PPMI) delivered remotely via telephone or video chat to improve pain and OUD treatment outcomes in the large, dispersed population of patients with OUD, including a sample of veterans - a highly vulnerable patient population that has been particularly hit hard by the opioid crisis and a priority population.

Objectives

The goal of the project is to conduct a hybrid Type I randomized effective-implementation trial of a modified Psychosocial Pain Management Intervention (PPMI) compared to an Enhanced Usual Care (EUC) condition both delivered by telephone or video chat. Both conditions have been specifically tailored to include educational topics (primarily the EUC material) and coping strategies (primarily the PPMI material) targeted towards patients receiving buprenorphine treatment for an OUD with co-occurring chronic pain, with the goal being to maximally reach and engage this population of patients to remain on buprenorphine treatment over 12-months. The primary and secondary aims are as follows:

Primary Aim 1: Conduct a randomized controlled trial (RCT) comparing a remotely delivered PPMI (n=100) to EUC (n=100) to assess the impact of randomization to PPMI on retention on buprenorphine treatment over 3-months.

Secondary Aim 1: Conduct a randomized controlled trial (RCT) comparing a remotely delivered PPMI (n=100) to EUC (n=100) to assess the impact of randomization to PPMI on retention on buprenorphine treatment over 12-months.

Secondary Aim 2: Determine the impact of a remotely delivered PPMI on pain level, pain-related functioning, and frequency of substance use over 3-months.

Secondary Aim 3: Determine the impact of a remotely delivered PPMI on pain level, pain-related functioning, and frequency of substance use over 12-months.

Secondary Aim 4: Facilitate the rapid implementation of results by gathering qualitative data from key stakeholders including MAT treatment providers (n=15) and patients who received the PPMI condition (n=20).

Design and Outcomes

This project will build off the work completed during the funded R21 phase of the project (grant *R21AT010106)* which was an observational, mixed-methods study focusing on the refinement and feasibility evaluation of this treatment protocol. Consistent with Stages 1A and 1B of the NIH Stage Model of Intervention Development, the work accomplished during the R21 phase provided all the

components necessary for this phase of the project, an RCT examining the efficacy of a remotely delivered (via telephone or video chat) PPMI intervention in retention on buprenorphine treatment over 12-months post study enrollment.

Participants (N=200) will be recruited from multiple community-based organizations and buprenorphine treatment clinics as well as the Veterans Health Administration (VHA). Patients presenting with treatment at the recruitment sites will be eligible to participate in the study if they report (1) experiencing at least moderate or greater self-reported chronic pain over the past 3-months, (2) beginning treatment for OUD with buprenorphine *(the term we use to refer to all buprenorphine products including buprenorphine/naloxone)* within the past 6-months, and (3) having regular and consistent access to a telephone and willingness to use that phone for study treatment sessions. Following the confirmation of study eligibility, participants will be consented and complete the baseline assessment, which will include a brief research staff administered interview, a self-report survey, and completion of a voluntary urine drug screen. Participants will be randomly assigned to receive one of the two study conditions (PPMI [n=100] vs. EUC [n=100]). The PPMI intervention consists of 8 individual therapy sessions intended to be completed via phone or video chat during the next 4-6 weeks. The EUC condition will consist of two brief educational sessions based around materials related to chronic pain and buprenorphine treatment delivered via phone or video chat during the next 4-6 weeks. Participants will meet with the research therapist for an introductory meeting upon enrollment to receive condition materials and schedule the phone sessions. Follow-up assessments for both conditions will occur immediately post-treatment (e.g. at 1-month post enrollment), and then again at 3-, 6-, 9- and 12-months post study enrollment. Participants will also be asked to complete weekly surveys over the first 13 weeks of the study.

The primary outcome of interest is retention on buprenorphine treatment, or continuation on buprenorphine treatment over three months. We are primarily interested in evaluating the proximal impact of PPMI on buprenorphine treatment retention. We will also evaluate the longitudinal (over 12 months) impact of PPMI of buprenorphine treatment retention as a secondary outcome. The primary outcome will be assessed using self-report measures (e.g. weekly surveys) and research administered interviews (e.g. TimeLine Follow Back). The secondary outcomes of interest are longitudinal (12 month) buprenorphine treatment retention, pain level, pain related functioning, and frequency of substance use, including opioid use. These secondary outcomes will be collected via self-report surveys, research administered interviews, and, when possible, urine drug screens. We will calculate means and standard deviations for these outcomes at baseline, 1-, 3-, 6-, 9- and 12-months, as well as change scores for the two groups.

Intervention Conditions and Duration

Individuals who are eligible and choose to participate in the study will be asked to complete a baseline enrollment assessment and will be randomized to a treatment condition (PPMI [n=100] vs. EUC [n=100]). In order to keep non-specific factors relatively consistent across study conditions, PPMI and EUC conditions are designed to be delivered over the same time interval (e.g. 4-6 weeks post study enrollment). Both conditions will be delivered by masters-level therapists and will follow a treatment manual. Therapists will receive extensive training to provide the PPMI condition and will also be monitored for adherence to the EUC condition protocol.

Participants meet with the study therapist by phone, video chat, or in person, when possible, following study enrollment and randomization to receive a brief introduction to the condition and the specific condition materials (e.g. a Participant Workbook for those randomized to the PPMI condition, and Educational Materials for those randomized to the EUC condition). All participants

will receive information regarding how to complete the study therapy or educational sessions via telephone or video chat to ensure confidentiality. The sessions for each condition (8 for PPMI and 2 for EUC) will be delivered over the phone or video chat to maximize engagement and reach for potential future implementation in rural areas with limited access to treatment. Following the completion of the study sessions, participants will participate in a total of 5 follow-up assessments (1-, 3-, 6-, 9-, and 12-months post enrollment). In addition to these follow-ups, during the first 13 weeks of the study (e.g. 3-months post enrollment and randomization), participants will be asked to complete weekly surveys to collect information regarding pain level, treatment retention, and general well-being. The total duration of time for participants in the study will be about twelve months.

PPMI Condition: The PPMI condition will involve 8 individual therapy sessions that will be delivered via telephone approximately 2 times per week over the course of about 4-6 weeks following study enrollment and randomization. The PPMI condition sessions are estimated to last 60 minutes each. These sessions have been developed by the study team as part of the prior R21 grant and will use a Cognitive Behavioral Therapy framework to provide coping strategies and information on how to manage chronic pain and remain engaged in buprenorphine treatment. The PPMI will also include additional content related to: substance use, retention on buprenorphine treatment (e.g. questions about whether the patient has taken recent doses of their medication or has remained engaged in care at the treatment clinic), a brief discussion of barriers/facilitators to buprenorphine treatment, as well as advice on ways to adhere to treatment, despite experiencing pain. Participants will be asked to provide feedback on the quality and relevance of the session material via a post-treatment self-report survey at follow-up.

EUC Condition: The EUC condition will involve 2 brief (5-10 minute) educational sessions delivered via telephone or video chat over the course of 4-6 weeks following study enrollment and randomization. The project therapist will review and discuss two brochures covering topics related to chronic pain and buprenorphine treatment with the participant, in addition to reviewing a study-developed resource guide. Thus, the EUC condition will provide some level of contact and education regarding relevant topics but will not overlap with the specific content of the PPMI condition. Participants will also be asked to provide feedback on the quality and relevance of the session material via a post-treatment self-report survey at follow-up.

Sample Size and Population

The target enrollment number for the RCT is 200 participants. Participants will be recruited from multiple community-based organizations and buprenorphine treatment clinics as well as the Veterans Health Administration (VHA). Of these 200 participants, 100 will be randomized to receive the PPMI condition (intervention condition) and 100 will be randomized to receive the EUC condition (control condition).

For this protocol, randomization to condition will be carried out by blocking on gender (male vs. female), past year use of heroin (yes vs. no), and veteran status (veteran vs. community). Computerized randomization will occur in blocks of randomly chosen sizes to equalize randomization over time and to prevent the possibility that staff could unwittingly manipulate subject assignment to conditions.

1. STUDY OBJECTIVES

1.1 Primary Objective

The goal of the project is to conduct a hybrid Type I randomized effective-implementation trial of a modified Psychosocial Pain Management Intervention (PPMI) delivered remotely compared to an Enhanced Usual Care (EUC) condition. To that end, the primary objectives of this project are:

Primary Aim 1: Conduct a randomized controlled trial (RCT) comparing remotely delivered PPMI (n=100) to EUC (n=100) to assess the impact of randomization to PPMI on retention on buprenorphine treatment over 3-months.

Hypothesis for Primary Aim 1: We hypothesize that participants in the PPMI (intervention) condition will have greater retention on buprenorphine treatment (i.e., lower treatment dropout) up to 3-months when compared to participants who receive the EUC (control) condition.

1.2 Secondary Objectives

The main objective of this project is to conduct an RCT of a modified psychosocial pain management intervention (PPMI) delivered remotely via telephone or video chat to patients with chronic pain who are participating in buprenorphine treatment for the management of an opioid use disorder (OUD). The ultimate goal is to have clear data on the short-term efficacy of the PPMI approach on buprenorphine treatment retention and pain level as well as data examining the long-term outcomes and implementation of this approach (i.e., using a Hybrid effectiveness-implementation design). In addition to the preliminary test of efficacy, a key secondary objective of this project will be to gain information on this important population (chronic pain patients with OUD who are newly engaged in buprenorphine treatment) to develop more effective future treatments. In addition, we will ask a group of participants and local buprenorphine providers a series of open-ended questions about their experiences. The semi-structured qualitative interviews will be conducted with key stakeholders, including both patient participants (n=20; following completion of the 12-month follow-up assessment) and providers/clinic staff (n=15) who are delivering buprenorphine treatment. The qualitative analyses of semi-structured interviews will help assess acceptability of the intervention by participants, identify key elements of the intervention for participants, and assess perceptions of barriers and facilitators to future adoption. With informed consent from the participants and providers, all interviews will be audio recorded and transcribed. To that end, the secondary objectives of this project are:

Secondary Aim 1: Conduct a randomized controlled trial (RCT) comparing a remotely delivered PPMI (n=100) to EUC (n=100) to assess the impact of randomization to PPMI on retention on buprenorphine treatment over 12-months.

Hypothesis for Secondary Aim 1: We hypothesize that participants in the PPMI (intervention) condition will have greater retention on buprenorphine treatment (i.e., lower treatment dropout) up to 12-months when compared to participants who receive the EUC (control) condition.

Secondary Aim 2: Determine the impact of a remotely delivered PPMI on pain level, pain-related functioning, and frequency of substance use over 3-months.

Secondary Aim 3: Determine the impact of a remotely delivered PPMI on pain level, pain-related functioning, and frequency of substance use over 12-months.

Hypotheses for Secondary Aims 2 and 3: We hypothesize that participants receiving the PPMI (intervention) condition will report (1) a decrease in the level of pain intensity, (2) an increase in pain-related functioning, and (3) a decrease in the frequency of substance use, over the 3-month follow-up period (Secondary Aim 2) and over the 12-mionth follow-up period (Secondary Aim 3) compared to the EUC (control) condition.

Secondary Aim 4: Facilitate the rapid implementation of results by gathering qualitative data from key stakeholders including MAT treatment providers (n=15) and patients who received the PPMI condition (n=20).

Hypothesis for Secondary Aim 4: We will follow a comprehensive plan to integrate quantitative and qualitative data to more rapidly enable future implementation of the intervention in patients receiving buprenorphine for OUD. First, this study is a mixed-methods hybrid type I study specifically guided by the widely-used RE-AIM framework, which provides essential elements to consider to understand barriers and facilitators to future implementation. We will address key specific questions that we will be able to answer through our qualitative and quantitative data and how they will inform our understanding of future implementation as guided by the specific elements of RE-AIM. Second, we are using a rapid analysis approach in our qualitative interviews, a specific deductive approach using semi-structured interviews to produce actionable information from qualitative data in a timely manner. We will organize the summarized qualitative data using matrices, which will increase efficiency of analyzing the data and synthesizing overall findings. Finally, our team has extensive methodological expertise in conducting mixed-methods substance use disorder intervention studies to enhance future implementation.

1.3 Exploratory Objectives

For this project, we will examine several pain-related constructs as potential mediators of the effect of randomization to the intervention on subsequent measures of our key outcomes. Specifically, we will examine the following:

Exploratory Aim 1: Explore the impact of early changes (i.e., baseline through 1-month) in self-efficacy to manage pain without the use of substances, pain catastrophizing, pain acceptance, and self-efficacy in managing buprenorphine treatment to the impact of a remotely delivered PPMI (intervention condition) on buprenorphine treatment retention and pain levels over the 3-month follow-up period.

Exploratory Aim 2: Explore the impact of changes throughout the 12-month follow-up period in self-efficacy to manage buprenorphine medications and confidence in buprenorphine treatment retention to the impact of a remotely delivered PPMI (intervention condition) on follow-up buprenorphine treatment retention and pain levels.

2. BACKGROUND AND RATIONALE

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

The US faces a public health crisis resulting from the increase in opioid prescribing for pain that has led to a record number of individuals who have developed an opioid use disorder (OUD). OUD is a debilitating illness associated with fatal overdose, suicide and numerous other serious harms. Medication assisted treatments (MAT) are effective in treating OUD and reduce overdose and

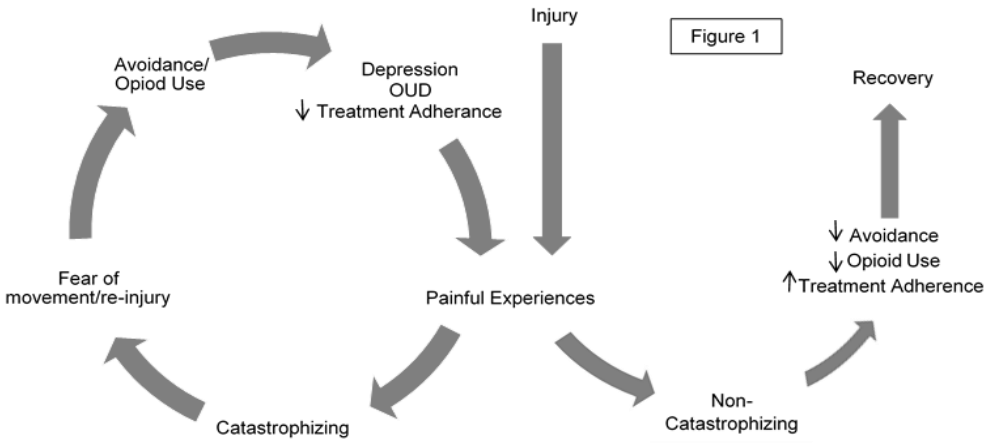
overall mortality. Recently, the 21st Century Cures Act, which supports the SAMHSA State Targeted Response (STR) to the Opioid Crisis grants, is helping to increase access and availability of these important treatments. However, even when MAT is available, poor retention in MAT is common and treatment drop-out is associated with a high likelihood of relapse to opioids. Difficulty coping with chronic pain plays a major role in the development of OUD as well as ongoing opioid misuse for many patients,[28-30] and the failure to successfully treat pain in OUD patients may be a key driver of treatment dropout in MAT patients. Alongside efforts to expand access to MAT for patients with OUD, there is a pressing need for novel non-addictive treatments for pain that can be implemented and disseminated to enhance the positive impact of MAT.

The need to enhance access to and the impact of MAT. The most effective long-established treatment for OUD is MAT with opioid agonists buprenorphine and methadone.[21-23] Initial studies of MAT were based on individuals receiving methadone, which required close monitoring with patients in regular (often daily) contact with treatment providers. Unlike methadone, buprenorphine (the term we use to refer to all buprenorphine products including buprenorphine/naloxone) can be prescribed by physicians in an office-based setting. Buprenorphine treatment is highly effective, associated with decreased overdose and decreased overall mortality,[31,32] and associated with improved Hepatitis C and HIV outcomes.[33,34] This increased feasibility of treatment could potentially increase the appeal of MAT as well as MAT adherence. Unfortunately, poor access to MAT and poor treatment adherence remain significant barriers to addressing the national epidemic of OUD.

Numerous efforts are underway to expand capacity to deliver MAT in the community. In 2017, Dr. Amy Bohnert, a colleague and close collaborator with Drs. Lin and Ilgen was awarded a grant from the state of Michigan through STR funds to develop the Michigan Opioid Collaborative (MOC), a multi-component program to increase the workforce of clinicians delivering MAT as well as referrals to these clinicians. The MOC uses a combination of care managers and addiction physician consultants to provide support to clinicians in the community to increase delivery of MAT. The MOC is established in four counties included within the Community Mental Health Partnership of Southeast Michigan (CMHPSM), which include rural, suburban, and metropolitan regions. However, even if this (and other similar projects underway throughout the United States) are successful in expanding treatment capacity so that patients can be identified and obtain MAT, poor treatment adherence remains a significant problem. Currently, rates of retention on MAT are close to 50% at 3 months on buprenorphine[24-27] and discontinuation is associated with not only a higher prevalence of relapse to opioid use but also high mortality.[31,35] Although there is some limited support for contingency management,[36,37] there is very little support for other behavioral interventions to improve MAT treatment adherence.[38] Newer and improved techniques are needed to address poor treatment adherence in order to optimize the positive impact of MAT.

Pain as a driver of opioid use and poor treatment adherence in MAT. Pain is highly prevalent among individuals receiving MAT, with prevalence rates often greater than 50% in patients receiving MAT.[4,5] When present, pain is associated with worse MAT outcomes including increased craving for substances and with increased illicit opioid use.[39-41] Many patients with OUDs view pain as a central part of the onset of initial OUD symptoms as well as the ongoing maintenance of opioid misuse.[28,42-44] Although these findings may partially reflect recall bias, they also clearly capture the fact that those with active OUD view pain as a key driver of substance use. Similarly, maladaptive reactions to pain likely influence engagement in adaptive behaviors central to recovery from OUD, including MAT adherence.

A psychosocial model of pain and substance use provides a framework for understanding the determinants of chronic pain, as well as the implications of pain-related coping for functional outcomes and treatment targets.[45] The fear-avoidance model of chronic pain was proposed by Lethem and colleagues,[46] and this theory has been expanded and adapted over time to apply to many different types of pain.[47,48] Within this approach (depicted in the left side of Figure 1), a cycle of negative outcomes is initiated when a specific painful stimulus causes an individual to consistently assume the worst, referred to as catastrophizing. This cognitive component of the model leads, in turn, to greater fear of re-injury, which increases the likelihood of avoidance of activities and the use of maladaptive coping strategies. We modified this model slightly to highlight the potentially problematic role of addiction in perpetuating negative outcomes among those with chronic pain.[49] The use of maladaptive coping strategies serves as the link between fear and more chronic negative outcomes such as disability, the development of OUD, and poor treatment compliance. This overall model has been used extensively for the past 25 years as part of most multi-dimensional treatments for pain, and cross-sectional results based on two large samples of pain patients found broad support for this model.[50] To the best of our knowledge, this relevant model has not been examined among individuals receiving MAT for OUD. Our operating hypothesis for this project is that the negative cycle around pain catastrophizing and poor pain-related outcomes can lead to general decreases in functioning as well as relapse to opioids leading to poor adherence on MAT treatment.[51] The hypothesis is that by targeting the intersection between negative cognitions related to pain and opioid use, the proposed intervention will improve OUD treatment adherence, opioid-related outcomes and pain functioning.



Treatment options for chronic pain in those with OUD. Over the past decade and a half, opioids have become the most-commonly used form of treatment for chronic pain. Despite the risks of use of opioids in those with substance use disorders, having a substance use disorder is associated with an *increased* likelihood of being prescribed opioids[52] as well as higher dose opioids.[53] Compton and Volkow[54] noted that one of the primary questions facing clinicians and researchers is "how should one treat pain in persons who have a history of addiction or those who already exhibit signs of addiction?" (pg.106). Given the elevated risk for poor outcomes among those with comorbid OUD and pain and potential concerns with the prescribing of opioids in this comorbid sample, there is a need to identify non-pharmacologic interventions for these patients.[55] These concerns are particularly pressing in those receiving MAT where, by definition, virtually all patients have a history of problematic substance use, and a large proportion of these patients also have difficulties with chronic pain.[56-61] Buprenorphine may be a particularly attractive option for patients with comorbid OUD and pain due to some evidence, though from mostly observational studies, to suggest that it

can also be effective in reducing pain in those with problematic opioid use or OUD.[62-65] However, given the recent evidence indicating that the addition of comorbid pain is associated with worse MAT outcomes, including increased craving for substances and with increased illicit opioid use among those receiving MAT,[4,39-41] additional strategies are needed to improve OUD treatment outcomes for patient with OUD and chronic pain.

Psychosocial pain management interventions are a particularly promising non-addictive option for pain management in those with OUD. Psychosocial interventions for pain are based on a biopsychosocial approach that incorporates the elements of the fear-avoidance model.[45,66] Cognitive Behavioral Therapy (CBT) and acceptance-based strategies are designed to address the factors leading to poorer functioning and maintenance of the negative cycle characterized by the fear-avoidance model (e.g., catastrophizing, behavioral avoidance, etc.[67,68]). The "exit strategy" from this negative cycle is represented on the right-hand side of Figure 1. Within this approach, a shift in perception of pain (i.e., from catastrophic to non-catastrophic) decreases fear and facilitates increased self-efficacy to manage pain, activity and recovery of functioning, without reliance on maladaptive strategies, such as substance use. Thus, when a change in cognition is coupled with more adaptive coping behaviors (e.g., increased healthy physical activity instead of opioid consumption), negative outcomes are reduced. Recent elaborations of CBT for pain have emphasized *pain acceptance* as an important target for therapy, and acceptance of pain is consistent with decreased catastrophic thinking about pain.[11,69-72] The overarching goal of these treatments is to assist in the development of an adaptive problem-solving approach based on a conceptualization of pain as controllable, acceptable, and/or tolerable.

This study is based on an integrated CBT/acceptance-based approach for pain management that emphasizes functional adaptations to pain, referred to as our Psychosocial Pain Management Intervention (PPMI). Psychosocial interventions have demonstrated efficacy for reducing pain and improving functioning in persons with a broad spectrum of pain-related conditions.[11,12] Psychosocial interventions are also associated with lower post-treatment pain and better functioning than wait list controls or other active control conditions.[11,73] A comprehensive meta-analysis of 25 trials indicated that CBT for pain produced significant reductions in pain and negative affect compared to wait list and attention control conditions.[12] CBT interventions were associated with a moderate effect size (of .5) despite a high degree of variability in the quality of trials and types of pain studied. Many of these studies strictly adhered to the CONSORT guidelines[74] and, thus, provided a strong test of the efficacy of the intervention. However, an unfortunate consequence of the methodological rigor of prior work is the frequent use of strict subject exclusion criteria; with the exception of our previous work, most prior trials involving CBT for pain have excluded patients with significant substance use. We have adapted a PPMI approach for patients with pain in addiction treatment.[49] Results from a recently completed trial indicate that receipt of the intervention was associated with significantly lower pain intensity, higher pain-related functioning, and lower alcohol use over 12-months relative to an attention control.[14] Moreover, individuals randomized to the PPMI approach reported significantly greater self-efficacy to cope with pain without using substances than did those in the control condition, and this is consistent with the underlying theoretical model that these changes in perception mediated the important improvements in pain and functioning. As noted in the commentary accompanying our recent *Addiction* paper on this study "Ilgen et al. report on an efficacious intervention integrating biopsychosocially oriented chronic pain therapy into addiction treatment. With benefit on both pain and substance use outcomes, … [this intervention] shows promise for larger effectiveness and implementation studies to address this widely prevalent and

growing clinical need."[75] Although based on a sample of individuals with different substance use disorders engaged in abstinence-based addiction treatment rather than MAT, with relatively modest modifications, this intervention could be particularly helpful for individuals with both chronic pain and OUD receiving MAT, and our existing PPMI protocol will be adapted for the MAT population to serve as the basis for the proposed work.

Reaching and treating patients on MAT with chronic pain. Although the SAMHSA STR grants will likely expand access, this brings additional challenges in delivering evidence based psychosocial treatments for pain, which have traditionally been delivered in-person. For these interventions to be feasibly delivered to patients across programs expanding MAT, new delivery strategies are needed. Telemedicine approaches offer an attractive method to reach patients with pain and OUD. Prior work, led by members of our research team, have demonstrated that telemedicine approaches for pain management can improve self-management and outcomes of patients with chronic pain and other chronic diseases.[76-78] These studies have repeatedly demonstrated that patients who are socioeconomically vulnerable are particularly receptive to CBT and similar interventions delivered by phone, and that such services can improve patient outcomes.[79-83]

Importance of improving OUD treatment in Veterans. As highlighted in the original call for SAMHSA STR proposals, Veterans are a key priority group for improving MAT outcomes. OUDs are common in Veterans who use VHA services with over 69,000 VHA patients diagnosed with an OUD in fiscal year 2017. Veterans also frequently experience opioid-related adverse outcomes. After accounting for differences in gender and age distributions, VHA patients have nearly double the rate of fatal overdose compared with adults in the general US population. Nonetheless, in 2015, 31% of Veterans with OUD in the VHA received pharmacotherapy for OUD. Despite the compelling need to increase access to OUD treatment, there are a number of factors that have made large scale treatment delivery challenging, particularly for those Veterans living at substantial distances from VA Medical Centers. Consequently, telemedicine-delivered interventions may be particularly useful. There is high prevalence of comorbid conditions including chronic pain, which is also associated with suicide and other adverse outcomes in the Veteran population. Thus, interventions addressing both chronic pain and substance use are critically needed to improve outcomes for Veteran with OUD.

Scientific rigor and guiding premise and justification for efforts to expand the impact of this work. From the completed pilot (R21AT010106), we learned key information that has guided the development of project materials. Specifically, we learned that participants with pain reported that pain impacts their ability to perform daily activities including spending time with friends and caring for family members, and also impacts their mood and quality of sleep. Participants, however, reported that despite still experiencing pain, they find taking their buprenorphine significantly helps reduce their pain level, in addition to taking other medications such as acetaminophen and ibuprofen, as needed. Interview data obtained from patients also suggested a long and varied history with substances, often beginning with the introduction to alcohol and other drugs in their teenage years and progressing to substance use disorders later in life. Many patients reported first being introduced to opiates through prescriptions obtained from their doctor as a result of an injury. This highlights the fact that, although the intervention focuses on opioids, it is also essential to discuss the co-use of other substances. Participants interviewed to date have identified substantial issues or problems with taking their buprenorphine such as hoarding or stocking up on their medication and taking their medication more or less frequently than prescribed. They reported positive effects of the medication, such as pain relief and mild euphoria, however; they have also

encountered problems that may deter them from remaining on their medication regimen. In terms of negatives aspects of taking buprenorphine, one participant expressed some negative experiences in self-help recovery meetings from individuals who did not believe that taking buprenorphine for the treatment of an OUD is an acceptable form of treatment. Another participant reported similar negative feelings coming from family and friends, who also view buprenorphine treatment in a negative way. One participant expressed frustration with the cost of the medication, as well as the availability and restrictions imposed by their insurance company on the type of medication they will cover (generic vs. brand name). These insights have helped to tailor specific aspects of the manual to include specific discussion of how to handle obstacles to remaining in treatment.

The information gathered from participants through qualitative interviews and beta testing highlights the high prevalence of pain and OUD. Consistent with our theoretical model, this information supports the guiding premise of this study that delivering an effective, non-pharmacological pain management intervention to adults receiving MAT for OUD would help to improve their pain level and functioning as well as increase retention on MAT. The findings have provided important initial data on a new strategy to treat pain in the large group of individuals on MAT with pain. The current RCT will expand the impact by including important modifications to address the following areas of key scientific and clinical significance:

The need to study longer-term outcomes and conduct strong tests of mediation. Substance use disorders in general, and OUD in particular, are best conceptualized as chronic relapsing conditions. Thus, developing an accurate picture of the symptoms and treatment of OUD requires the collection of longer term follow-up data. Given this, many of the seminal studies of OUD treatments involve longer term follow-ups of 6- and/or 12-months. Beyond direct tests of intervention effects, longer term follow-ups that include multiple measures of hypothesized mechanisms of action of the intervention allow for stronger tests of mediation. Specifically, establishing the appropriate temporal ordering, in which changes in the hypothesized mediators are measured prior to subsequent clinical outcomes, are key to determining whether those hypothesized mediators underlie any effects of random assignment to condition on outcomes. For the proposed study, it is our underlying hypothesis, guided by the literature, that the telephone based PPMI condition will lead to greater improvements in pain and that these improvements will, in turn, be associated with improvements in treatment retention and substance use outcomes. The ability to spread out measurement of these constructs over the course of the trial facilitates substantially improved testing of these hypothesized mechanisms of change.

The ability to move rapidly to implementation of evidence-based interventions. Given the critical need for interventions to improve treatment and retention among patients with OUD, interventions improving OUD treatment outcomes need to be designed incorporating pragmatic elements that can lead to more rapid implementation. Using a mixed methods approach that integrates quantitative data on outcomes with qualitative data from key stakeholders will provide information not only on the effectiveness of the intervention, but also help explain quantitative findings related to effectiveness and mechanisms of action of PPMI. The Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) framework will be used to understand barriers and facilitators to future implementation. RE-AIM is a robust tool that is widely used to examine impacts of health behavior interventions. The proposed study will use a hybrid effectiveness-implementation design (Type 1), incorporating the RE-AIM framework to examine the effectiveness of the intervention and collect additional information on barriers and facilitators to inform future

implementation efforts.

The project is highly innovative for a number of reasons. First, despite the fact that there has been a long-standing interest in the intersection between pain and opioid use, to date, we are unaware of any studies that have examined the impact of a psychotherapeutic pain management approach in those with pain in MAT for OUD. The application takes a pragmatic approach to investigate whether a psychotherapeutic pain management intervention could help adults stay on OUD pharmacotherapy, decrease substance use and increase pain functioning. Second, this project will extend the impact of the study by expanding recruitment to include the high-risk group of Veterans with OUD over a long follow-up period. Third, this proposal builds on efforts (led by this team) supported by SAMHSA State Targeted Response to Opioid Crisis funds to increase MAT access through expanding the capacity of primary care and other providers to increase delivery of MAT. Thus, the intervention proposed will support efforts of primary care and other frontline clinicians to feasibly deliver MAT, by developing a non-addictive option for managing comorbid pain and to increase treatment retention. Fourth, with the critical push to disseminate MAT widely, it has become crucial for treatment to not only be efficacious, but also to be able to be practically delivered. We are specifically examining delivery of the PPMI intervention via telephone or vide chat to be able to reach the dispersed population of patients with OUD that can now be treated with the expansion of MAT. Finally, the project is designed to facilitate an important mediator analysis to determine whether the proposed mechanisms of action of the intervention account for any observed changes in MAT retention and substance use over the follow-up interval. Overall, this project combines numerous innovative elements in its topic area, focus, and methods to address and better understand co-occurring pain and OUD in the community and veteran populations.

2.2 Study Rationale

This trial builds on observational work by our team and other researchers that highlights the high prevalence of pain and OUD, as well as randomized trials that demonstrate the efficacy of psychosocial interventions for pain in different patient populations, including those receiving addiction treatment. Consistent with our theoretical model, the guiding premise is that delivering an effective, non-pharmacological pain management intervention to adults receiving MAT for OUD would help to improve their pain level and functioning as well as increase retention in MAT. This trial would be the first to study an integrated CBT/acceptance-based approach for pain management in a MAT population, examine feasibility of remote delivery of the intervention and begin to estimate the potential impact on subsequent pain and MAT outcomes. These findings would provide the knowledge base needed to identify viable methods to treat pain in the large group of individuals who have developed OUD.

Developing, refining and testing behavioral interventions in adults with substance use disorders. The study team has a long history of NIDA-, NIAAA, VA- and DoD-funded research developing and delivering interventions to individuals with substance-related problems. The prior and ongoing work of the research team has been conducted in several different types of care settings (Emergency Departments, inpatient psychiatry, substance use disorder treatment programs), addresses a wide range of age groups, a range of target behaviors (alcohol/drug use, treatment engagement, suicide prevention, pain, etc.), has generally involved interventions integrating CBT approaches with other treatments (e.g., adaptations of motivational interviewing), and has typically had follow-up assessment with retention rates ranging from 80%-95%. Overall, our team has been successful in refining and adapting behavioral interventions for those with substance use disorders, recruiting

participants into randomized trials and achieving high long-term follow-up rates in these individuals. We have been actively engaged in research to examine the role that health systems play in opioid prescribing and opioid-related adverse outcomes. Our initial work, published in 2011 in *JAMA*, established a link between higher prescribed opioid dosage to increased risk unintentional overdose.[84] Subsequent work also found a similar link between opioid dosage and increased risk of suicide.[85] Our recent analyses of all patients with pain receiving opioids in the Veterans Health Administration, demonstrated that health system-level policy changes can have an impact on high-dose opioid prescribing.[86]

Opioids and opioid related harms. We have been actively engaged in research to examine the relationship between opioids and adverse outcomes and the roles that clinicians and health systems play in opioid-related adverse outcomes and MAT treatment. Our work has examined links between opioids and increased risk of suicide[6,79,80], unintentional overdose,[5,73,81], and factors contributing to opioid use and misuse such as mental health disorders and chronic pain,[82-84] including in clinical samples of patients with substance use disorders.[85,86] Dr. Lin's recent work includes studies of a national sample of buprenorphine providers to assess treatment practices,[87] which shows the majority of buprenorphine providers, especially primary care providers, highly value adjunctive psychotherapy but report their settings do not have adequate resources to provide services to buprenorphine patients with complex psychosocial needs.[88] These results indicate additional ways of delivering psychosocial treatment are needed.

Supporting expanded access to MAT for Michigan Providers. In the Spring of 2017, SAMHSA released special funds to support specific programs under the State Targeted Response to Opioid Crisis program. Dr. Pinals, is the Director of Behavioral Health and Forensic Programs for the Michigan Department of Health and Human Services (MDHHS), clarified that the state of Michigan was most interested in projects that utilized evidence-base strategies to expand the reach and impact of MAT in the state via support to healthcare providers. Dr. Amy Bohnert has worked with Drs. Ilgen and Lin to design a project called the Michigan Opioid Collaborative (MOC). Briefly, this program provides: (a) funding for providers/prescribers obtain the DEA waiver necessary to provide MAT, (b) support for MOC-enrolled MAT providers via same day consultation with a specialty Addiction Physician to help with any questions or concerns that arise while delivering MAT, (c) access to Behavioral Health Consultants to provide psychosocial supports for patients receiving MAT, linking them to other resources, as necessary. The project is designed to be scaled-up to the full state of Michigan and the use of telephone consultations and remote supports for providers will significantly increase access to MAT to patients living in remote areas of Michigan, often many hours' drive from an Addiction Physician or Opioid Treatment Program. However, in the first year of funding, the program has concentrated on the 4-county region immediately surrounding Ann Arbor, MI. To facilitate connections with local providers, the MOC team partners with the Community Mental Health Partnership Southeast Michigan (the CMHPSM), which provides oversight and management of all addiction treatment services for all Medicaid patients in the 4-county region. The CMHPSM is extremely supportive of this project.

Pain and addiction. Dr. Ilgen has conducted research over the last 10 years examining the link between pain and addiction. Our early analyses of patients in opiate substitution treatment programs indicated that over half of all patients in this sample reported significant pain at baseline, and those with pain at baseline continued to have more severe problems in other domains of functioning at 1-year follow-up.[59] Additional work described the positive association between pain

and substance use disorders in the general US population and highlighted the potential bidirectional relationship between pain and addictions.[87] In separate work, we documented the extremely high prevalence of recent misuse of opioids among US adults in addiction treatment – 68% of the overall sample.[88] We have also shown that lower pain acceptance is associated with higher severity of OUD, further supporting the utility of PPMI in OUD patients with comorbid pain; yet, there is currently limited use of non-pharmacological treatments for pain in addiction treatment patients.[89,90] Beyond these observational studies, we have also studied the impact of interventions to improve pain in those with substance use disorders. We recently completed a VA-funded (Ilgen, PI) trial of an intervention for pain (which will serve as the basis for the proposed PPMI intervention) versus EUC in VA patients (N = 131) receiving substance use disorder treatment. Over 95% of participants provided data during at least one of the follow-up assessments; 87% completed the 12-month follow-up. In addition, data indicate that the intervention was successful in modifying pain- and substance-related outcomes. Over the 12-month follow-up, randomization to the CBT intervention predicted significantly lower pain levels [β(se) = -0.65(0.29); p<0.05)], improved pain-related functioning [β(se) = 0.25 (0.11); p<0.05] and lowered frequency of alcohol consumption [β(se) = -0.77; p<0.01].[14] Similarly, we received support of NIDA to conduct a randomized trial of this intervention in a non-VA residential addiction treatment setting. We are in the process of completing the manuscript on this study but follow-up rates for the study were high – 1-month: 91%; 3-month: 78%; 6-month: 85%; 12-month: 87%. The findings are consistent with the VA trial and show an impact of the intervention on improved pain-related functioning and reduced alcohol use. Overall, prior work on this topic is consistent with the proposed theoretical modal and the central hypothesis of the proposed study that addressing pain with an evidence-based intervention will improve outcomes in those with addictive disorders.

Telehealth delivery of CBT for pain is feasible and improves outcomes. The study team has experience delivering behavioral health interventions over the telephone for a number of conditions, including pain and suicide. In particular, Dr. Piette (co-I on the current project) has extensive experience developing and evaluating interventions using telephone care and mobile health systems to improve self-management and outcomes of patients with chronic pain and other chronic diseases (see biographical sketch).[76,77,91] His expertise in this area will be essential in helping the study team overcome common barriers to telehealth delivery (e.g., Dr. Piette already has thorough existing protocols for: scheduling calls in flexible way to increase adherence, how to record calls to use for supervision, developing systems for tracking call data, etc.). Dr. Piette's prior studies have shown repeatedly that patients who are socioeconomically vulnerable are particularly receptive to CBT and similar interventions delivered by phone, and that such services can impact patients' outcomes.[79-81,83,91] Our studies consistently indicate that many patients engage actively in telephone-delivered psychotherapy and self-management assistance. In a recent comparative effectiveness trial among VA patients with chronic pain (Piette, PI; Ilgen, Co-I), those receiving telephone CBT completed an average of 8.9 out of 10 possible sessions compared to 6.6 sessions among patients randomized to face-to-face treatment (p<.001).

Opioids and OUD treatment in Veterans. Our team is composed of individuals with joint appointments as Research Investigators at the VA Ann Arbor Center for Clinical Management Research, a VA Health Services Research and Development Center of Innovation with extensive research on opioid and other substance-related issues in Veterans.[6,79-81,91,92] Our initial work establishing the relationship between opioids and adverse outcomes were conducted in Veteran

populations. Our analyses of all patients with pain receiving opioids in the VHA, demonstrated that health system-level policy changes can have an impact on high-dose opioid prescribing.[91] Our recent work stresses the ongoing importance of addressing opioid-related harms with findings of substantial increases in opioid overdose rates in the population of Veterans receiving care in the VHA in recent years.[93] Finally, Dr. Lin's (MPI) ongoing experience delivering buprenorphine treatment to Veterans with OUD in the VA Ann Arbor Healthcare System will help inform the intervention and help with participant engagement and recruitment.

Conducting Mixed Methods research. The study group has extensive experience conducting mixed-methods implementation research. Multi-PI Dr. Ilgen was formally a workgroup leader of the VA's national substance use disorder Quality Enhancement Research Initiative (QUERI), which was focused on implementing evidence-based practices into VA care. The proposed project involves the use of a hybrid type I effectiveness-implementation design to provide additional information to speed the implementation of the intervention. The team includes Dr. Fetters, a national expert in the mixed-methods approach needed for this study design. He is a family medicine physician and Chief Co-Editor of Journal of Mixed Methods Research who has led mixed methods studies in complex clinical settings for over 20 years. He will oversee the iterative conduct and analysis of the qualitative interviews, and guide interpretation and integration with the quantitative study findings in order to enhance future implementation of the intervention.

Summary of prior research by the study team. The study team has crucial skills that will ensure successful recruitment, intervention delivery, self-report and objective data collection, analysis, and dissemination of study results. Of core relevance to the proposed work, much of this prior work was conducted in the VHA, involved the use of longer-term follow-ups with rates exceeding 80%, and incorporated content expertise in implementation science. This strong team has been augmented through the addition of Dr. Fetter, a national expert in the use of mixed-methods in clinical research.

3. STUDY DESIGN

The overall goal of this 4-year project is to conduct a randomized controlled trial (RCT) of a modified telehealth-based Psychosocial Pain Management Intervention (PPMI) for patients with an opioid use disorder (OUD) and co-occurring chronic pain receiving buprenorphine treatment. The PPMI will be tested against a brief, supportive psycho-educational control condition, Enhanced Usual Care (EUC), to determine changes in buprenorphine treatment retention (primary outcome) and pain- and substance-related variables (secondary outcomes) between conditions. The PPMI condition uses elements of Cognitive Behavioral Therapy (CBT) for pain management and substance use adapted specifically for patients with OUD newly engaged in buprenorphine treatment. A total of 200 patients with chronic pain who recently began treatment with buprenorphine (within the prior 6 months) will be enrolled into the trial. Participants will be recruited from multiple locations including community based outpatient substance use treatment clinics, outpatient medical clinics in which a provider is able to prescribe buprenorphine for the treatment of an OUD, substance use clinics that are affiliated with the VA HealthCare System, and from various locations in the community (either via posted flyer or website advertisements). After enrollment, participants will be randomly assigned to one of the two conditions - 100 participants will receive the PPMI and 100 participants will receive the EUC condition. Participants will be randomized using a stratified block design on biological sex, opioid use history (past year use of heroin), and veteran status. Therefore, this study will have 8 possible strata: Community men with a past year history of heroin use,

Community women with a past year history of heroin use, Community men with no past year history of heroin use, Community women with no past year history of heroin use, Veteran men with a past year history of heroin use, Veteran women with a past year history of heroin use, Veteran men with no past year history of heroin use, and Veteran women with no past year history of heroin use. Following randomization, participants will complete treatment sessions based on random treatment assignment. The PPMI therapy condition consists of 8 individual therapy sessions. The EUC condition consists of 2 educational sessions reviewing brochures on chronic pain and buprenorphine treatment, in addition to study developed information and resource brochure. All sessions will be delivered via telephone or video chat by a master's level therapist. Each treatment condition has been manualized in order to ensure the treatment sessions are standardized, focused, and therefore more easily disseminated following the trial completion. Condition sessions have been modified to be delivered remotely (via phone or video chat) in order to maximize treatment engagement and test the feasibility of providing tele-based therapy to participants with OUDs and chronic pain. Participants will be re-assessed at follow-up study visits immediately following study condition delivery 1-month post enrollment, and then again at 3-, 6-, 9, and 12-months post study enrollment. Participants will also complete a weekly survey for the first 13 weeks after study enrollment. Knowledge generated in this study will have important implications for improving outcomes for patients with OUD and chronic pain through increased understanding of effective patient-focused psychosocial strategies to help patients better manage pain.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

The project will recruit individuals currently receiving buprenorphine for the treatment of an opioid use disorder (OUD) who also report experiencing moderate to severe chronic pain. The goal is to identify and recruit participants from various states throughout the country. We will use several strategies to identify potential clinics including utilizing contacts with the Community Mental Health Partnership of Southeast Michigan (CMHPSM) and the Michigan Opioid Collaborative (MOC; Dr. Amy Bohnert, PI) and identifying high prescribing providers within each state. Study staff will be in communication with staff on MOC (including Dr. Lin) to identify new and existing MAT waivered providers in the area who would be interested in participating in our study as a recruitment site. In order to prescribe or dispense buprenorphine, clinicians including physicians, nurse practitioners and physician's assistants must qualify for a DEA X-waiver, which includes completing additional hours of required training. MOC works directly with the clinicians to guide them through the process of obtaining a waiver to prescribe or dispense buprenorphine. Additionally, study staff will be in communication with clinics and organizations across the country to participate as a recruitment site and/or display our flyers in community locations. As a recruitment site, clinic and organization staff will discuss the study details with potentially eligible participants, provide our flyers, will provide a letter of support, and be listed as a site on our study's IRB.

We currently have identified 10 clinics that will serve as recruitment sites for the RCT:

(1) **The University of Michigan Healthcare System,** Ann Arbor, MI. The University of Michigan Healthcare System, with an emphasis on the Back and Pain Center and Addiction Treatment Services (UMATS), has a comprehensive approach to pain care and utilities evidence-based techniques, including MAT, for the diagnosis of OUD and treatment of chronic pain.

(2) **Meridian Health Services – Community Programs, INC.**, Waterford, MI. Meridian Health Services offers residential therapy-based addiction treatment and detox management in addition to a variety of outpatient programs at several locations throughout southeast Michigan. Meridian Health Services has served as a recruitment site for several other RCTs conducted by the PIs of the project, including a large scale RCT (N=510) of patients with chronic pain.

(3) **Packard Health**, Ypsilanti, MI. Packard Health offers outpatient addition treatment services through the combination of MAT and behavioral therapies to help sustain recovery in addition to a variety of other outpatient programs.

(4) **Gammons Medical**, Richmond, Warren, Royal Oak, Waterford, and Wayne, MI. Gammons Medical is an addiction medicine practice with locations throughout Eastern Michigan. They focus on treating patients with substance use disorders and they have numerous physicians, nurse practitioners, and physician assistants who are buprenorphine-waivered and provide MAT to patients with OUD.

(5) **Best Medical Services, PLC,** Traverse City, MI. Dr. David Best is a buprenorphine-waivered physician who provides treatment for patients with chronic pain and opioid use disorder.

(6) **Spectrum Health Medical Group**, Grand Rapids, MI. The Spectrum Health Medical Group is a large multidisciplinary physician group, with a specialized Addiction Medicine Program that provides MAT to patients in addition to other recovery treatment services.

(7) **VA Ann Arbor Healthcare System (AAVA),** Ann Arbor, MI. AAVA provides healthcare services to veterans in southern Michigan and northern portions of Ohio. This system contains providers who supply MAT services to veterans in this region.

(8) **Dr. Michael L. Fox, DO**, Addiction Medicine, Livonia, MI. Dr. Fox is a buprenorphine-waivered physician who provides MAT, detox, pain management and treatment of mood disorders to patients with chronic pain and opioid use disorder.

(9) **Dr. Andreas Sidiropoulos, MD**, Ann Arbor, MI. Dr. Sidiropoulos is a buprenorphine-waivered physician who focuses on the treatment for substance use disorders by providing MAT.

(10) **Dr. Arun Gupta, MD,** Monroe, MI. Dr. Gupta is a buprenorphine-waivered physician who specializes in primary care services with a substance use treatment component, providing MAT to persons with opioid use disorders.

Each clinic has provided a letter of support for this project and has providers on site who prescribe buprenorphine to patients. We have selected a variety of clinics across the country to attempt to widely sample a variety of patients. Since the project is also actively enrolling only new buprenorphine patients (e.g. those completing a new buprenorphine induction and/or starting a new treatment episode following a lapse in medication usage) at the recruitment clinic site within the 6 months prior to study enrollment), we understand that we will need to recruit from a variety of clinics to ensure there are enough potential participants to approach for recruitment in order to achieve our target enrollment goal in the timeline provided. We anticipate remaining in close

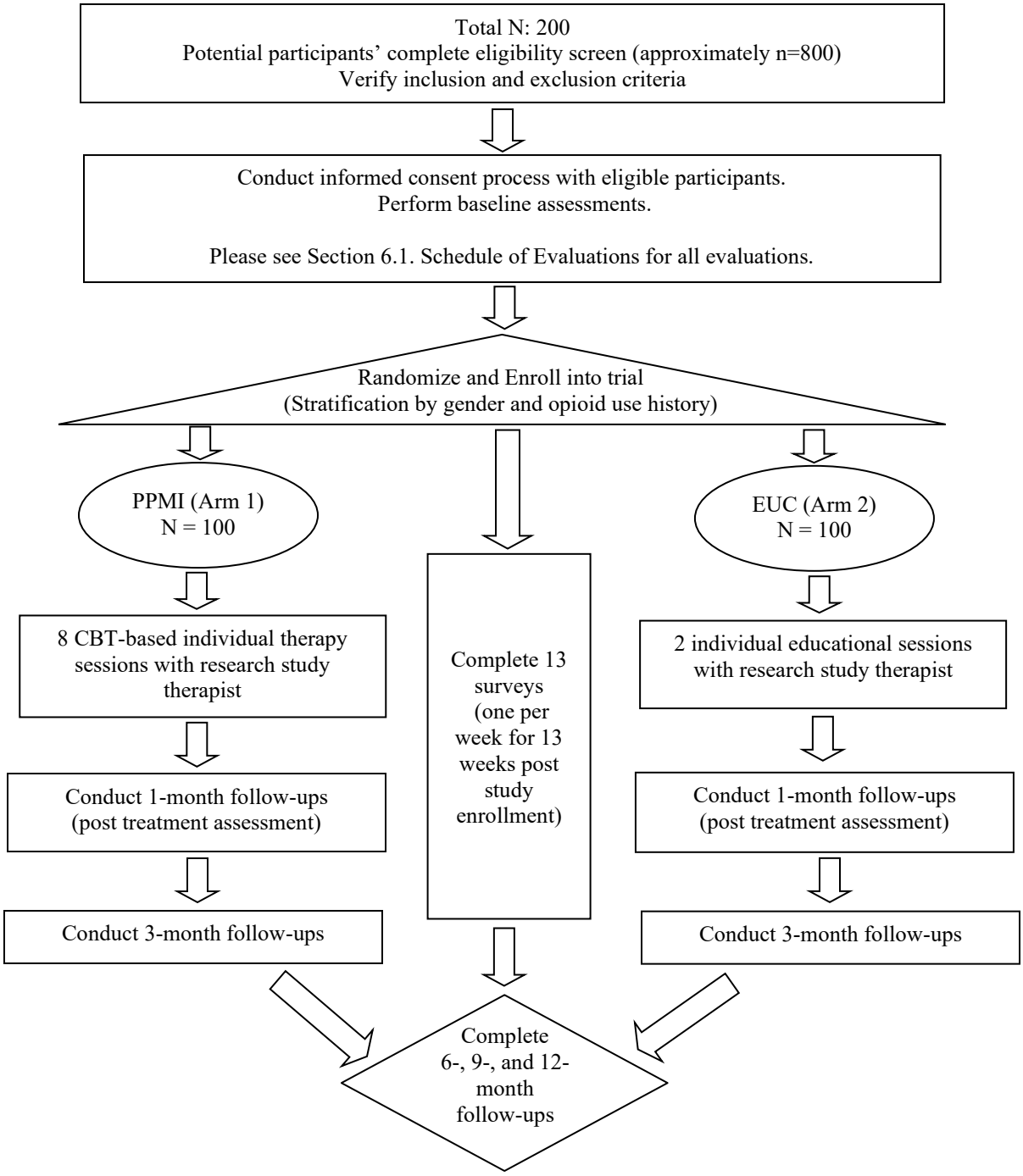
contact with colleagues at MOC to enlist new clinic sites if necessary, as the study progresses. In order to be sure that we are reaching the widest range of eligible participants, in addition to the recruitment sites listed above we will also recruit interested participants from the community who may learn about the study through posted flyers or online advertisements. These flyers and/or advertisements will be displayed in community locations (with appropriate permissions from the business owners) such as coffee shops, small businesses, restaurants, shops or stores, and/or pharmacies, or websites and will invite participants to contact study staff to learn more about the study and participate in the eligibility screening through the study website, a direct survey link, and/or QR code. As a community location, clinic or organization staff would be asked to display our flyer only but would not be provided with details about the study to have discussions with potential participants and would not be listed as a site on our study's IRB. Additionally, a study description with contact information may be included in recruitment site and community newsletters distributed to patients receiving MAT.

Planned enrollment rates for this phase of this project are based on current rates of opioid overdose deaths by race/ethnicity in Michigan, as well as the actual enrollment of our previous project with individuals with co-occurring pain and substance use disorders recruited from a residential treatment program in Michigan. The study sample is designed to be broadly representative of patients in Michigan who are being prescribed buprenorphine for the treatment of an OUD. All eligible participants receiving buprenorphine treatment at the recruitment sites will be approached for participation, regardless of gender or minority status. If we have an excess number of potential participants to approach at any given time during the recruitment window, we will prioritize recruitment of women and minorities whenever possible. For the Veteran sample, there was an average of approximately 270 patients diagnosed with OUD receiving buprenorphine at the Ann Arbor VA in 2018. With a one-year drop-out rate higher than 50%, an estimated 135 are new patients per year. We conservatively estimate that, out of both community and veteran participants, 50% of patients who complete the eligibility screen will have begun buprenorphine treatment within the past 6 months, 50% of those participants will have pain, 90% will meet criteria for an OUD within the past 12 months, and 80% will consent to the study (based on our prior work). This should be more than enough potential participants to make the proposed study feasible. However, if for some reason we have difficulty recruiting participants, we will expand recruitment to other nearby VA Medical Centers (e.g., Detroit VA is approximately 50 miles away) and/or we will expand our contact with additional MAT providers. Specific strategies will be used to identifying potential participants at each recruitment site. Due to the varied location and nature of the recruitment sites, several strategies may be applied at each site to ensure all potential participants are reached for recruitment. For additional details regarding recruitment strategies, please see Section 4.3 'Study Enrollment Procedures' below.

In practice, we anticipate that we will need to screen about 800 individuals (goal of 200 randomized/50% eligibility rate based on pain/90% eligibility rate based on OUD diagnosis/70%eligibility rate of new buprenorphine induction/80% consent rate). We estimate that 80% (n= 160) will provide follow-up data for self-reported outcomes. This is based on our prior work in addiction treatment patients utilizing various retention strategies tailored specifically to this population. It is worth noting that we will calculate our primary outcome (treatment adherence) conservatively and may assume that lost to follow-up is non-adherent. Thus, we will have follow-up data on 100% of those randomized for our primary outcome. We anticipate the following racial and ethnic composition of the sample: approximately 74% White, 18% Black, 3% American Indian/Alaska

Native, 3% Asian, and 1% Native Hawaiian or Other Pacific Islander. Approximately 7% of the sample for this study is estimated to be of Hispanic ethnicity. We anticipate that approximately 41% of the sample will be female in the community population and 10% of the veteran sample will be female. Regarding female participants specifically, we estimate that of the community sample, approximately 76% will be White, 20% will be Black, 2% American Indian/Alaska Native, and 2% Asian. Approximately 7% of the female sample will be of Hispanic ethnicity. We estimate that of the female veteran sample, approximately 60% will be white, 20% will be Black, 10% will be American Indian/Alaskan Native, 10% will be Asian. Approximately 10% of the sample will be Hispanic. Figure 2 below describes the recruitment and enrollment flow expected for participants into this study. To ensure the rigorous conduct of this study, we will utilize the CONSORT checklist and flow diagram to document participant accrual, flow and retention at all stages of the study across all recruitment locations.

Figure 2: Study *Flow Diagram for Persist Study RCT*



4.1 Inclusion Criteria

Participant responses to study measures will be evaluated by research staff to ensure all eligibility criteria are met before participants are enrolled into the full RCT. Participants will complete a brief eligibility screening survey to ascertain appropriateness for the study. Any questions pertaining to participant responses will be clarified with the participant prior to the determination of eligibility status. The ability to understand study procedures and to comply with them for the entire length of the study will be assessed prior to enrollment in the trial.

Inclusion criteria for the main RCT trial are:

(a) at least legal adult age to consent without a guardian ((18 years of age or older in all states except Alabama (requires 19 years of age), Nebraska (requires 19 years of age), and Mississippi (requires 21 years of age))
(b) having a diagnosis of an OUD within the past 12 months;
(c) started buprenorphine *(the term we use to refer to all buprenorphine products including buprenorphine/naloxone)* treatment within the past 6 months
(d) at least moderate or greater self-reported pain on average over the past 3 months;
(e) regular and consistent access to a telephone and willingness to use the phone for study telephone sessions.

Participants in this study will be of legal adult age to consent without a guardian (18 years old or older in most states unless in Alabama (requires 19 years of age), Nebraska (requires 19 years of age) and Mississippi (requires 21 years of age) for several reasons. All participants will be patients prescribed buprenorphine for the treatment of an OUD who also experience pain. Due to the differences in pain management and intervention strategies for those 17 and younger relative to older individuals, a separate study would be required to appropriately examine opioid safety among children and adolescents age 17 and under with pain. Individuals age 18 to 20 will be included in the study because individuals in this age range receive medical care services related to OUD and pain in the same manner as those individuals age 21 and older.

Participants will be eligible for the study if they report experiencing symptoms that would indicate a clinical diagnosis of an OUD within the past 12 months. This will be evaluated by the participant's responses provided on the Structured Clinical Interview for DSM-5 (SCID-5), a semi-structured interview guide for making the major DSM-5 diagnoses, including substance use disorders. Participants will be eligible for the RCT if they meet criteria for at least a mild severity OUD according to this measure. Participants will also be eligible for the RCT if they report taking buprenorphine as pills, tablets, or films (excluding injection and patch routes of administration) specifically for the treatment of an OUD. Participants previously engaged in buprenorphine treatment who report a lapse in medication usage of at least 30 consecutive days within the previous 6-months will be eligible for the study since we will consider the resuming of the medication a *new treatment episode*. In addition, participants must report taking at least one dose of prescribed buprenorphine within the 10 days prior to the enrollment assessment interview to be eligible for the trial. There are other instances in which buprenorphine may be prescribed such as the immediate management of opiate withdrawal symptoms (as is usually seen in detoxification centers). For this study, since retention on buprenorphine treatment is the primary outcome of interest, participants will not be eligible for the study if they are only receiving buprenorphine for detox and do not plan to continue the treatment past the opiate withdrawal phase. In addition, participants will not be eligible for the study for similar reasons if they are prescribed longer-acting

forms of buprenorphine such as the injectable form or patch form, as these administration methods do not follow similar retention metrics as the pills, tablets, or films.

Participants will be eligible for the RCT if they report experiencing at least moderate pain within the past 3-months. This will be measured via participant self-report by an average score of 4 or greater on responses provided on the Numeric Rating Scale of Pain Intensity [NRS-I]. The cutoff score of 4 or greater has been used in previous work by the trial investigators in large scale RCTs of individuals with chronic pain and is also supported by the literature as a good representation of at least moderate pain. Finally, participants will be eligible for the study if they report having consistent access to a phone that could be used for therapy sessions. While participants will be monetarily compensated for cost associated with using their phone for the treatment sessions, the participants must be willing to use an electronic device to complete the sessions in order to be eligible for the study. The option to video chat will be offered to participants but is not required for participation.

Participants will be eligible to participate in the trial regardless of any medications they may be taking at the time of enrollment, however participants must have an active buprenorphine prescription from a treatment provider and must report taking their prescribed buprenorphine medication at any time within 10 days of the study enrollment interview to be eligible for the trial. The decision of what medications to use will be made by the participant's treatment provider and will not be influenced by study participation. Thus, the relationship between risks and benefits of buprenorphine in this population are not changed by participation in the study. To increase representativeness of the sample, we do not have any additional criteria related to contraception use for this study and participants will be retained in the study if they become pregnant during the follow-up period.

To accomplish **Secondary Aim 4** (qualitative interviews for rapid implementation), a random sample (n=20) of participants who completed the PPMI condition will be interviewed in addition to a sample (n=15) of buprenorphine providers.

Inclusion criteria for Secondary Aim 4 are:

- For RCT study participants:

  (a) completion of the at least 2 sessions of the PPMI condition
  (b) consent to participate in future research

- For clinic stakeholders:

  (a) at least 18 years of age or older
  (b) being a currently waivered provider of buprenorphine for OUD or other clinic staff at time of recruitment

4.2 Exclusion Criteria

In addition to the review of participant responses for eligibility criteria, all participants will be reviewed to ensure that no exclusionary criteria are present prior to study enrollment and randomization. Due to the sensitive nature of this study, the Coordinating Center PIs (Drs. Ilgen and Lin) will have final discretion in the inclusion/exclusion of participants.

Exclusion criteria for this study are:

(a) under the age of 18 years old in most states, or under the age of 19 in Alabama and

Nebraska and under 21 years of age in Mississippi;
(b) an inability to understand English;
(c) an inability to provide voluntary, informed consent;
(d) buprenorphine medication prescribed in the form of a monthly injection and/or a transdermal patch
(e) self-reported pregnancy at the time of study enrollment
(f) currently residing outside of the United States

This study does not intend to include minors or obtain parental consent for minors. Individuals under the legal adult age to consent without a parent/guardian (age of majority) in their state will be excluded. Given that we are recruiting nationally, this includes excluding those under age 18 from most states, those under age 19 in Alabama and Nebraska, and those under age 21 in Mississippi.

Individuals will be excluded from participation if they are unable to understand English. Accommodations to study procedures (e.g. reading study survey questions aloud to the participant) can be made for participants with hearing or visual impairments to ensure that they may be able to participate in the study if willing and able to do so. Since the therapy sessions and all study assessments will be delivered in English only, participants must demonstrate an ability to comprehend the English language to be able to adequately complete study requirements. Additionally, participants recruited through study advertisements on online websites who report currently living outside of the United States will be excluded from participation in the RCT.

Participants must also be able to provide voluntary, informed consent in order to participate in the full RCT. Individuals who are under the guidance or care of a legal guardian and are incapable of providing informed consent without the legal guardian or representative will be excluded. Likewise, individuals suspected of competence issues (e.g. individuals with reported severe Traumatic Brain Injuries, severe untreated psychosis, intoxication, acute suicidality, etc.) will be evaluated by research staff to determine appropriateness for inclusion in the study. These criteria are meant to ensure that participating patients will be capable of benefiting from a therapy intervention delivered remotely. Decisions about these exclusion criteria may be made using a combination of self-reported symptoms and researcher's judgment in consultation with clinician investigators. Participants may be given a brief mental status examination to determine their current competence level before being enrolled into the study. Participants who present to the enrollment appointment intoxicated and unable to provide consent will be asked to reschedule the assessment for another date, at which time the participant may be enrolled if all eligibility criteria are met.

Women who report that they are pregnant during the eligibility screening will be excluded from initially participating in the study because: (a) of the additional clinic services they are likely to be receiving; and (b) we are unlikely to have sufficient numbers of pregnant women to facilitate meaningful subgroup analyses. Women who become pregnant during the course of the study will be allowed to continue with participation as study interventions and visits are not known to cause any increased harm to the mother or fetus.

Patients who are receiving buprenorphine medication in the form of a monthly injection or transdermal patch will be excluded from participating in the study. Participants will not be excluded based on current or previous substance use or other mental health diagnoses. Participants will be allowed to continue all prescribed medications during the course of the study. Participants who arrive to study visits clearly under the influence of alcohol or other substances will be evaluated by

the research staff using the approved Intoxicated Participants protocol in order to determine whether or not the participant is capable of continuing with the study visit. If the research staff deems the participant is not able to continue, the visit will be rescheduled and the participant will be provided with the necessary resources to remain safe. Similarly, participants who present to study visits experiencing active suicidal or homicidal ideation or behaviors, acute psychosis, or emergent medical issues (e.g. active, acute withdrawal or overdose) will be evaluated by research staff. If necessary due to the severity of the concern, the appointment will be rescheduled for a later date and the research staff will assist the participant in accessing necessary clinical and/or medical care. Details on the safety protections for participants will be discussed in detail below in Section 7. "Safety Assessments" and can also be located in the study Data and Safety Monitoring Plan (DSMP), and the study specific Manual of Operations (MOP) and Standard Operating Procedures (SOP).

4.3 Study Enrollment Procedures

This study will utilize a wide range of recruitment strategies to ensure the recruitment of a representative participant sample of national buprenorphine patients. Participants will be actively recruited by research staff from multiple buprenorphine treatment clinics throughout the community and the VA HealthCare System that prescribe buprenorphine for the treatment of OUDs. All identified buprenorphine treatment recruitment sites will have providers who are waivered to prescribe buprenorphine for the treatment of substance use disorders and are currently accepting new patients at their clinic. Participants will also be passively recruited through posters, flyers, ads, videos, newsletters or brochures that will be displayed within approved treatment clinics and community locations (e.g. coffee shops, gyms, community centers, restaurants, libraries, stores or small businesses, pharmacies, churches, etc.), or through website advertisements and/or a study specific website. All study specific flyers, posters, videos, ads, newsletters, or brochures posted or made available at various locations or websites (with appropriate approval from the location or business owner) within the community will be IRB approved prior to displaying. These recruitment materials will have information on how potential participants may contact the research team to learn about the study, or may provide a link or QR code that will direct participants to the study website or to the online eligibility consent and survey. Given the fact that the recruitment sites and/or posted flyers will be in a variety of geographic locations, we will utilize several different recruitment strategies to ensure that all potential participants are being captured within the recruitment phase. All steps in the study enrollment and recruitment process are outlined below and will be explained in the study's Manual of Operations (MOP) and site specific SOPs for reference. All activities pertinent to study recruitment will be documented and tracked using the study Screening Eligibility Log. This log will aid research study staff in identifying and tracking potential participants, will contribute to the construction of both the main study CONSORT diagram at the conclusion of the study, and provide data necessary to report to funding agencies (NCCIH) or Independent Monitoring Committees (IMCs) regarding participant accrual rates.

Recruitment strategies at any location may include the following (where applicable):

1) reviewing patient medical records to pre-screen for eligibility (where permitted by recruitment clinic site and approved by the IRB; a Waiver of HIPAA Authorization for access to protected health information for screening purposes and any additional documentation necessary will be obtained);

2) approaching potential participants in-person at a recruitment site, which may include approaching patients at intake/orientation meeting(s), group meetings, individual appointments, scheduled appointments, or in waiting areas;

3) recruiting potential participants through posters, flyers, and/or brochures placed at the recruitment sites or social media pages, included with patient paperwork provided by the recruitment site or treatment provider, and/or displayed within the community (at locations such as coffee shops, gyms, community centers, restaurants, libraries, stores or small businesses, pharmacies, churches, etc.)

4) recruiting potential participants through a study specific website, which includes an embedded eligibility survey;

5) recruiting potential participants through a page on UMHealthResearch.org, a website hosted by the Michigan Institute for Clinical and Health Research (MICHR). Participants who learn of the study through UMHealthResesearch.org will be redirected to the study website and the direct link to the survey through the study's description. If someone with a UMHealthReserach.org account finds the study and expresses interest in participating, they may be contacted by research staff by phone, email, or text.

6) contacting interested participants through mail, e-mail, and/or text message (in cases in which potential participants are not approached at the recruitment site) with appropriate follow-ups via phone or video chat when necessary;

7) referrals from treatment providers at the recruitment clinic sites or from behavioral health consultants affiliated with the MOC program;

8) recruiting potential participants through newsletters distributed by recruitment sites and community listservs for patients receiving MAT treatment

9) recruiting potential participants through the use of social media/online platforms, including but not limited to: Facebook, Instagram, Twitter, Craigslist, Reddit, Google, ResearchMatch.org, and InTheRooms.com. These will serve as the launching pad for targeted, social media and online advertisements and is approved by IRBMED.

10) recruiting potential participants through google ads;

11) recruiting potential participants by posting our brochure, flyers, or newsletter language on social media in population specific groups (i.e. medication assisted treatment information & support group).

For potential participants recruited from the University of Michigan Healthcare System or through the VA HealthCare System (when, approved by the IRB and any additional oversight entities), patient medical records will be screened by research staff to identify patients with upcoming clinic appointments or inpatients who have had addiction consult services who may be eligible for the study. Research staff will review records of patients currently receiving treatment services to identify those patients who have a current buprenorphine prescription, an OUD diagnosis, or at least moderate or greater reported pain, as well as other inclusion/exclusion criteria including age or mental incompetence. The University of Michigan patient records will be accessed via MiChart, the University of Michigan Healthcare System's fully integrated, patient-centric electronic health record (EHR) system. Potential Veteran participants will be identified for recruitment using The VA's Computerized Patient Record System (CPRS), the VHA medical record

system. The research team has extensive experience obtaining pre-screening eligibility information from CPRS from prior studies. We request a Waiver of HIPAA Authorization to access PHI to screen patients to determine eligibility only. Patients who enroll in the full study will complete an informed consent process that may include HIPAA authorization which will allow for access to PHI during the study. Results of record reviews will be kept in a Chart Review Log, which identifies which records have been reviewed, the preliminary eligibility of the patient, and the outcome of the contact with research staff (e.g. approached, enrolled, declined, ineligible, etc.). Conducting preliminary eligibility screening with the HIPAA waiver prior to contacting participants will help streamline the recruitment process and eliminate approaching or contacting ineligible patients or those who have already declined participation in the study, thus reducing the burden to patients and staff. Also, the waiver will allow for research study staff to conduct preliminary eligibility screening independent from treatment providers at the clinic, which will allow for the integrity and equality of the recruitment process to be maintained without potential biases. We will use pre-study identification numbers to store the information gathered and will follow all safeguards outlined in our IRB application for protecting confidential information.

Within these healthcare systems, identifiable data will be used for recruitment purposes. This may include patient names, addresses and phone numbers, and will be securely maintained on restricted servers in an access-limited folder, with access given only to the specified research study staff members responsible for recruitment (such as the project managers or other research assistants). This information will be maintained in a separate folder from other study data files. All recruitment data will be stored on secure computer servers, accessible only by approved study staff. Any paper documents with identifiable patient information will be kept in a locked file cabinet in a locked office. The investigators will destroy subject identifiers upon completion of all recruitment activities, or as soon as an applicable VA Records Control Schedule allows, whichever is latest. Due to the repeated involvement of individuals in substance use treatment services and the long recruitment timeframe, it is important that research study staff retain identifiable information on patients until the end of the recruitment period to ensure that research study staff are not re-contacting participants who have stated they were not interested in participating in the study, have already agreed to participate, or were otherwise ineligible. Once potentially eligible participants are identified via the pre-screening review, study staff will send an IRB approved recruitment letter via mail, email, or text message to potential participants explaining the study. Study staff may also attempt to contact the participant in person at an upcoming clinic appointment to explain the study. If in-person recruitment is not feasible, following the letter, email, or text message, study staff may attempt to contact the potential participant by phone to explain the study further and confirm eligibility.

Potential participants (either identified through pre-reviews of the medical records, approached at the treatment site during regular treatment programming, or referred from a treatment provider) may be approached by research study staff in-person at the recruitment sites. All potentially eligible individuals seen for appointments at the recruitment sites on days of active recruitment will be invited to learn about the study and participate in the eligibility screening. Research study staff will attempt to approach patients prior to or following their scheduled treatment appointment times as to not interfere with their care. Potential participants that have been referred from a treatment provider may be met in the waiting area of the clinic without their provider present or may contact or be contacted via phone by study staff about their interest. For potential participants recruited from community locations through flyers, newsletters, or the study website, the project postings will

have the contact information of the study staff displayed. Potential participants may contact study staff via email, phone, or text message and will be screened for eligibility by the study staff member following that contact. When identifying and interacting with potential participants, research staff will identify who they are and for whom they work. All recruitment materials approved under UM IRBMED will include a statement that the project has been approved by the UM IRBMED and will include the project Human Subjects Identification (HUM) Number. Specific procedures and materials for recruitment and consenting at VHA clinics will be approved by the VA Ann Arbor IRB.

When interacting with potential participants the research staff will present a brief explanation of the study by following the recruitment script, which includes information regarding the purpose of the study, the voluntary nature of the study, and the anticipated time commitment for the study procedures. Eligible patients who would like additional time to consider participation or who do not have time to meet with research staff on a particular day may be contacted by study staff at a later date either in person, or via phone, e-mail, or text message. For those interested in participating, the research staff member will provide the potential participant with the study materials to complete the eligibility screen. Since recruitment may occur in waiting rooms or other clinic locations which may not be private, interested participants will be asked to complete the electronic eligibility consent and a short eligibility survey via a tablet (or verbal consent and paper survey version if the participant desires) to ensure their answers will be kept private. This survey will allow the research study staff member to quickly determine eligibility for the RCT. Once the survey questions have been completed, a screen will appear informing them of their eligibility status. After participants return the tablet, the staff member will then be able to view if the participant is eligible or ineligible based on their responses. For those participants who choose to complete a paper survey, the research staff member will be responsible for determining study eligibility based on the participant's answers to the survey questions. Eligibility will be communicated directly to the participant by the study staff, and those who are ineligible will be thanked for their time and their participation will be completed. For participants who screen ineligible, those who screen eligible but are not interested in continuing with the study, or those who do not provide additional contact information, no identifiable information will be collected, however responses to survey questions will be retained to aid in monitoring of study accrual rates throughout the study. For participants who call the main study office or are approached via phone, the research staff member may either (1) obtain verbal consent (with approved waiver of documentation of informed consent) and verbally deliver the eligibility screening questions to the participant to determine eligibility, (2) direct the participant to the main study website to access the eligibility consent and survey, or (3) provide a link to the survey via e-mail or text message to the participant. Those participants who are not eligible based on their responses will be thanked for their time and their participation will be complete. No identifiable information from participants who screen ineligible will be collected following completion of the survey, however responses to survey questions will be retained to aid in monitoring study accrual rates throughout the study. The study contact will also be documented in the Screening Eligibility Log. VA participants will be tracked in a separate log maintained on the VA server. No identifying information or crosswalk information for VA participants will be stored at UM.

If in-person contact at the study site is not feasible, potential participants may learn about the study through study posters, flyers, newsletters, or brochures displayed at recruitment sites and/or community locations. Providers may also include study flyer information to participants during appointments. Potential participants may also learn about the study through advertisements posted on websites (e.g. social media sites, organizational webpages, etc.). These advertisements may be in

the form of study graphics, banner ads, email blasts, social media posts, or study specific video advertisements. Study advertisements, as well as flyers, newsletters, and brochures will indicate that the study is recruiting individuals with chronic pain who have recently been prescribed buprenorphine to participate in a study exploring new programs. Recruitment materials will include both the main study or local site phone number and the main study or local site e-mail address for potential participants to contact research study staff to gain more information regarding the study. Additionally, the recruitment materials will contain the web address for the main study website (https://umpersiststudy.org) and may also contain a link or QR code that will direct potential participants to the study eligibility consent form and eligibility screening survey. The website will serve as a resource for potential participants and will contain general project information, contact information, and national resources. The website will also provide a link to an online e-consent for screening (waivers of documentation of consent will be obtained) and a link to the REDCap survey. No identifying information will be collected directly on the website. All data and identifying information will be collected and stored on the REDCap survey platform. E-consents will be accessed through the REDCap survey platform and participants will have the option to print or save a copy of the informed consent information sheet before moving onto the brief eligibility screening survey. If the eligibility screening is completed in person or over the phone, the participant will provide verbal consent and be given the option to receive a paper consent for their records. For participants who respond to the study flyer via the main project e-mail, return correspondence will be sent to the e-mail address used by the participant providing them with a link to the study website which contains the eligibility consent and survey. Additionally, if other contact information was provided by the participant (e.g. the participant includes a return phone number in their e-mail response) study staff may contact them using the provided information in order to explain the study. Each prospective participant will enter the REDCap survey portal from the link provided in the recruitment e-mail. Before participants can complete the survey questions, they will be asked to review the e-consent and indicate their willingness to participate by selecting the appropriate response option. During initiation of the eligibility survey, each participant will be assigned a unique study ID number by REDCap. As noted previously, the electronic survey will be designed to determine eligibility based on the predetermined study criteria. Once all eligibility questions have been answered, all participants who screen ineligible will receive a thank you page ending their participation. No identifying information will be collected from those participants who are not eligible for the RCT. Reasons for ineligibility will be retained and recorded on the Screening Eligibility Log.

For participants who screen eligible, there will be a page that informs them of their eligibility for the study (if completing the survey electronically) or they will be verbally informed by the research staff member regarding their eligibility status. If recruitment is completed in-person or over the phone with a research staff member, the research staff member will confirm all eligibility criteria have been met prior to continuing with the recruitment script. The page (or recruitment script if verbally delivering the information to the participant) will provide information about the RCT. If completing the survey remotely, eligible participants will be asked to provide their name and contact information (phone number and e-mail address) and will notify the participant that a research staff member will contact them regarding the study and schedule an enrollment appointment. If in-person or over the phone, research study staff will schedule the appointment with the participant, collect contact information so that we can contact them regarding any changes to that appointment, and discuss video chat options for future appointments. Participants may choose the video chat platform most convenient for them (e.g., Zoom, BlueJeans, FaceTime or Skype for Business) for assessments and condition sessions, however, HIPAA compliant platforms (e.g.,

Zoom) will be recommended and encouraged. The initial enrollment appointment will be scheduled to be completed remotely over the phone or via video chat, however a participant may request an in-person meeting at a time and place that is convenient for the participant (e.g. the treatment clinic, their home, or a mutually agreed upon community location such as a restaurant, coffee shop, or library). These options will be discussed with all participants who have screened eligible and interested in participating in the study. Eligibility status for all participants will be documented in the Screening Eligibility Log as well as the Screener Inclusion-Exclusion Case Report Form. Information included in these documents will include the recruitment site the participant was recruited from, the type of recruitment (in-person, phone, e-mail, letter, website, newsletters, referral, etc.), and the eligibility status. The Inclusion-Exclusion Case Report Form must be completed prior to enrolling the participant into the full RCT in order to ensure that all inclusion criteria have been met and no exclusionary criteria exist. Any questions regarding study eligibility will be directed to the Project Managers and/or PIs prior to the consent and enrollment of the potential participant into the trial. The Inclusion-Exclusion Case Report Form will also be reviewed and monitored by the Project Managers for accuracy and completeness on a regular basis.

At the enrollment appointment, participants will first complete the informed consent process prior to participating in any study activities (written for in-person appointments, verbal consent with waiver of documentation for phone appointments). Trained research staff will conduct the informed consent process in-person, over the phone or video chat. Since this is a multisite project, the consent process for sites covered under the IRBMED will include a two-part document that will be reviewed with the participant: Part 1 of the consent document is the multisite portion of the consent which describes the study design and procedures; Part 2 of the consent document describes any *site specific* information that is different from or in addition to the information included in Part 1. Approval of the informed consent documents (both Part 1 and Part 2) will be obtained from the Institutional Review Board at the University of Michigan (who will be serving as the single IRB of record for the multisite project), NCCIH, and any additional regulatory bodies as necessary. Informed consent process and documents for VHA participants will be approved by the VA Ann Arbor IRB. Individuals interested in participating in the study will be given/sent the consent document, if possible, to have on hand to review with the research staff member. During this process, participants will be informed of the general nature of the study, what their involvement entails (which will also include information about randomization, the study arms including audio recording, and baseline and follow-up assessments), the risk/benefits, and limitations to confidentiality. As part of the informed consent process, participants will be told that participation is voluntary, that they can withdraw at any time, and that this will not impact their treatment. The limits of the NIH Certificate of Confidentiality will be explained in the consent form, but study staff will also verbally explain the limits of confidentiality (e.g. acute suicidal or homicidal intent, reports of child or elderly abuse, the need for immediate medical attention). Patients will also be made aware of any potential conflicts of interest that exist between study team members.

Additional study materials such as information sheets or resource brochures may be provided to the participant at this time in order to review relevant study procedures in a concise manner with the participant. As part of the consent process, participants will be given the opportunity to indicate if they would be interested in being contacted for further research. Any participant who responds positively will be considered for future studies (including participation in the qualitative interviews described in Specific Aim 4 of the project). For those participants who do not wish to participate in future research, their responses will be tracked and they will not be contacted for any future

studies. After reviewing the consent form documents with the participants, research staff will ask if he/she has any questions regarding their participation or the study requirements and limitations. Participants will also be asked to describe to the research staff member the essential elements of the study to ensure understanding. Any participants who are not interested after the review of the consent documents will be thanked for their time. Any participants who request more time to review the consent form documents or consult with others will have the opportunity to do so. These patients will be contacted by research staff at a later time or will able to contact research staff themselves. Those interested in participating will be asked to provide written or verbal informed consent. Participants who are not able to provide informed consent due to diminished mental capacity (e.g. acute intoxication or other impairment based on the judgement of the research staff member) or who are under the legal authority of a guardian prohibiting them from making health care decisions without a representative present will not be eligible for the study and will be thanked for their time. When providing written informed consent, participants will be given a signed copy of the consent form documents and the signed originals will be filed in a locked cabinet in a limited access area in the participant's confidential research file at the main study office. For those providing verbal consent, study staff will record that verbal consent was obtained. If a participant was not able to receive an electronic copy of the consent to have on hand to review during the phone consent process, they will be sent a copy by mail or email after consent is received. Study staff will review the consent form documents tracking for accuracy and completeness and complete the Consent Documentation Case Report Form before beginning any study procedures.

Once a participant has provided informed consent, they may begin the baseline assessment with the research administered interview to confirm eligibility (e.g. the presence of an OUD diagnosis of at least mild severity within the past 12 months as measured by the Structured Clinical Interview for DSM-5). Participants will not be considered enrolled in the trial until full eligibility has been confirmed. Those who do not meet criteria for a diagnosis of an OUD of at least a mild severity within the past 12 months will be notified they are not eligible for the RCT, thanked for their time, and receive study payment for the assessment. Eligible participants will continue and complete the remaining parts of the baseline assessment, be considered enrolled into the trial, and will be eligible for randomization. Following the completion of all baseline study activities, participants will be randomly assigned to either the PPMI or EUC conditions. Stratified random assignment to intervention (PPMI) and control (EUC) conditions will be employed by gender (operationalized as biological sex assigned at birth), past year use of heroin (yes/no), and veteran status (community/veteran). While utilizing multiple randomization blocks can complicate the enrollment process, there is evidence that the trajectories of treatment retention and outcomes varies between men and women, as well as between those with history of heroin use versus those without heroin use. The project biostatistician will guide the randomization process. To prevent the possibility that staff could unwittingly manipulate patient assignment to treatment, a computerized randomization technique will be used, wherein the odds of treatment assignment change, based on the immediately preceding assignments, but odds are not truly fixed, as in strict balancing. Sequential runs of assignment to one condition are possible but are equalized by the end of a randomization block of participants. Randomization to conditions will be monitored by the Project Managers in conjunction with the project PIs and biostatistician to ensure that conditions remain balanced and will revisit the blocking procedures should any imbalances occur during the trial.

Secondary Aim 4: Enrollment of participants and providers for qualitative interviews

To accomplish Secondary Aim 4 at the conclusion of the RCT, we will conduct qualitative interviews with key stakeholders including MAT treatment providers (n=15) and patients who received the PPMI condition (n=20). Providers who prescribe buprenorphine for the treatment of OUDs and other clinic staff from community clinic study sites (n=15) will be included Community providers will be approached through relationships established throughout the study's progress. Research staff will reach out to the provider directly via e-mail or in-person and invite them to participate in the interview. Qualitative interviews with providers will take place during Year 3 and Year 4 of the project. Specific interview questions will be drafted once the study has commenced in order to be sure we are collecting relevant information during the interviews. Research staff will set up a time to meet with the provider at a convenient location (e.g., their clinic or another specified place) or by telephone or video chat (based on the provider's preference) and will complete the informed consent process with the provider. Providers will be informed about the study purpose, the voluntary nature of the study, and that their responses will be kept confidential. Providers who provide verbal informed consent will then complete the qualitative interview, following which their participation will be competed. Stakeholder participants will be provided a copy of the consent form.

Persist RCT study participants will be eligible to complete the qualitative interview following completion of their 12-month follow-up study visit. Only participants randomly assigned to the PPMI condition who complete at least 2 of the 8 therapy sessions and agree to participate in future research will be eligible to participate in the interviews. We expect to enroll 20 participants recruited from the community participant population. Participants interested and eligible for the interviews will meet with a study staff member by phone, video-chat or in-person to complete the informed consent process and be asked for verbal consent before completing the interview. After the interview, participation will be complete. Participants will be provided a copy of the consent form.

5. STUDY CONDITIONS

5.1 Conditions, Administration, and Duration

Participants will be randomized following completion of the baseline (enrollment) assessment to receive one of the two study conditions: The Psychosocial Pain Management Intervention (PPMI; active intervention condition) or Enhanced Usual Care condition (EUC; control condition). The initial content of the PPMI condition's manual related to pain management existed for adults receiving substance use disorder treatment and has been utilized in previous RCTs; however, the content was modified to fit within a new setting, to be delivered over the phone or video chat, and to address issues specific to adults receiving buprenorphine. During the R21 funding period of this project, the PIs and project managers drafted initial detailed protocols and manuals for the PPMI and EUC conditions. Each of the existing sessions was re-written to fit with delivery via phone or video chat and to emphasize management of pain without using illicit opioids and buprenorphine adherence and retention. Since the prior manuals were developed to generally focused on all substances (mostly alcohol, cannabis and opioids), these manuals have been re-written to focus specifically on opioids and the ways in which poor pain, and coping with pain, relate to engagement in and adherence to buprenorphine treatment. Both manuals were then beta-tested and participant feedback was collected regarding the session content and the acceptability and feasibility of participating in therapy session over the phone. Currently, manuals for both conditions have been

finalized based on feedback received and received IRB approval.

Structure of PPMI and EUC condition delivery

In order to keep non-specific factors relatively consistent across conditions, PPMI and EUC will be delivered with the assistance of a manual and over the same time interval. Both conditions will be delivered by masters-level therapists trained specifically on the study treatment manual content. In order to effectively and efficiently deliver both conditions, the same study therapists will be trained to deliver both conditions. The PPMI conditions will involve 8 individual therapy sessions meant to be delivered via phone or video chat approximately 2 times per week over a total of 4 - 6 weeks. The EUC condition will involve two brief, educational sessions delivered via phone or video chat approximately once every 2 weeks (biweekly) over a total of 4 – 6 weeks. Participants will have a total of 6 weeks post study enrollment to complete all study sessions (8 total for PPMI condition, 2 total for EUC condition). Participants will not be allowed to complete any condition sessions following that 6-week deadline in order to ensure the maximum completion of the 1-month follow-up study visit.

Following randomization, participants will briefly speak with the study therapist to receive an introduction to their assigned study condition (either PPMI or EUC) and will receive the specific condition materials (i.e. a Participant Workbook for those in the PPMI condition, a study developed resource guide, a study timeline and payment FAQ sheet, and two brochures on pain management and buprenorphine for those in the EUC condition). This first encounter with the study therapist in each condition will be conducted in person, whenever possible, at the clinic where their buprenorphine provider is based or at a location in the community in order to provide the participant with session materials and to build rapport between the therapist and participant in order to increase the likelihood the participant will engage in the remotely delivered sessions. If in-person is not possible, study therapist will speak with the participant by phone and discuss the option of video chatting for future session. Each of the 8 PPMI sessions are estimated to last approximately 60 minutes each, whereas the 2 EUC sessions will likely last between 5-10 minutes each. Following the initial interaction for both conditions, the sessions will be delivered via phone or video chat to maximize engagement and reach for potential future implementation in rural areas with limited access to treatment. Participants will be provided information regarding how to contact the study therapist for their sessions and instructed to complete the sessions in a quiet location where they are relatively free from distractions in order to allow for maximum engagement with the study materials. Study therapists may end sessions early or reschedule sessions at their discretion if they feel continuing is not in the best interest of the participant (e.g. if a participant reports they are driving or currently using substances during the session). Any missed or incomplete sessions will be rescheduled for a later date. Participants will provide feedback on the quality and relevance of the session material (both PPMI and EUC) via a post-treatment self-report survey at follow-up.

Although the PPMI is the active intervention condition being tested during the trial, the EUC condition is designed to match the PPMI condition in terms of the non-specific aspects of receiving support and information regarding buprenorphine and pain management, therefore this project was designed to be a direct comparison between PPMI and an EUC condition. This design was chosen because limited data exist on the longer-term efficacy of the PPMI approach in individuals with OUDs and chronic pain receiving buprenorphine treatment, and no other short-term approach has evidence in terms of buprenorphine related outcomes supporting its efficacy in this population. The first and most important step in this line of research is to establish that the intervention is efficacious. This study design, then, provides a clear comparison group to determine whether or not

main effects may be due to the intervention components and not merely contact with a therapist.

Intervention receipt

Determining the level of intervention receipt among participants will be established through various methods. Straight session attendance will be calculated by summing the number of sessions the participant completed. From here, participants may be categorized into those who received no study condition (e.g. completed zero sessions in either the PPMI or EUC condition), those who received a partial dose of the study condition (e.g. completed fewer than 4 sessions for the PPMI condition and only 1 session for the EUC condition, or those who received the full dose of the study condition (e.g. completed all 8 sessions for the PPMI condition and 2 sessions for the EUC condition).

Content of PPMI and EUC conditions

The **PPMI condition** will follow the manualized treatment protocol previously developed by our study team and modified for this study as noted previously. The 8 session format delivered two times per week allows for a standardized progression with content built upon the previously presented treatment materials. The sessions will be delivered via phone or video chat and when using video chat, the research therapist will have the ability to display the condition materials if needed. The condition manual includes an introduction session consisting of education on the Cognitive Behavioral Therapy (CBT) treatment modality and how pain, buprenorphine treatment, and substance use are related. The main theme of the treatment is to provide participants with new ways of thinking and coping skills related to managing pain and opioid use in order to increase the likelihood the participant may remain in buprenorphine treatment. All sessions follow a general CBT framework which incorporates education, in-session skill building, and practice activities to be completed outside of the session. The treatment culminates in a final session consisting of a review of pain management and buprenorphine treatment retention skills as well as an exercise in relapse prevention and a review of resources. Each session will begin with a brief check-in and an outline of how the specific topic for the day (e.g., behavioral activation) relates to the psychosocial model of pain, opioid use, and buprenorphine treatment retention. Additionally, a review of previously assigned practice activities will occur in each session in order to allow the participant to express feedback on how they have been able to utilize the skills learned during the session outside of the treatment sessions. The manual is structured so that each session discusses some pain related content and no single session will be focused exclusively on pain, opioid use, or buprenorphine medication adherence/retention. Instead, content related to pain management, opioid use and buprenorphine treatment will be integrated into each session. Opioid misuse is primarily conceptualized as a maladaptive coping response and the treatment will address this by increasing the use of more appropriate coping skills and encouraging buprenorphine adherence/retention to treatment to increase stability. Based on our experiences, we modified the PPMI condition content to be appropriate for participants receiving medication assisted treatment specifically for an OUD. Participants in the PPMI condition will receive a Participant Workbook with necessary treatment materials during the in-person, introductory meeting. If participants are unable to locate their workbook, or request duplicate materials, they will be provided to the participant via e-mail or mail whenever possible.

In terms of specific content areas, the concept of acceptance is an overarching theme that is emphasized across all sessions in the PPMI condition. This approach generally highlights the importance of identifying specific goals for better functioning and working towards these goals during treatment. Additionally, several sessions incorporate acceptance into their content by way of activities and discussion of the willingness to acknowledge harmful coping versus healthy coping and

nonjudgmental description of emotions, thoughts, and situation that influence the ability to implement healthy coping skills. The aspect of treatment focused on cognitions includes sessions on thought monitoring, cognitive reconceptualization and cognitive restructuring. The behaviorally-oriented content includes sessions on behavioral activation (also used as a method to address pain and decrease depression), mindfulness techniques such as Progressive Muscle Relaxation, and attention diversion. Pacing, or strategically planning to avoid over-activity, is another behaviorally-oriented theme that will be presented and emphasized.

The **EUC condition** is designed to match the PPMI condition in terms of the non-specific aspects of receiving support for pain, substance use, and receiving monitoring of buprenorphine adherence. We have used modified versions of attention control conditions in two studies of pain (one funded by VA HSR&D and one funded by NIDA) as well as our work on suicide prevention in those with substance use disorders (one prior NIDA R21 and one ongoing study funded by the Department of Defense). The EUC condition for this study will involve 2 brief sessions (5-10 minutes in length) delivered via phone or video chat in which the study therapist will discuss a study-developed resource guide and two brochures (one on chronic pain and one on buprenorphine treatment) with the participant. When using video chat, the research therapist will have the ability to display the condition materials on the screen. The participant will be asked if they have any questions related to the material presented in the brochures and will provide education and support to the participant during the brief session. Thus, the EUC condition will provide a comparable level of contact with a study therapist who will provide support on topics that are relevant to the participant, however the materials will not overlap with the content of the PPMI condition. Patients randomly assigned to the EUC condition will receive the condition materials (e.g. brochures with the resource guide) during the initial in-person meeting with the study therapist, when possible. If unable to meet in person, the study materials will be emailed and mailed to the participant. While not directly intended to be therapeutic in nature, these brief sessions may help patients to better understand the origins and consequences of pain and substance use in their life. Topics related to psychological factors associated with pain and possible psychosocial coping mechanisms will not be a part of the formal content of the sessions.

Treatment as Usual

Both the PPMI and EUC conditions will be overlaid onto an episode of OUD treatment with buprenorphine at an outpatient clinic. While we will be recruiting from multiple predetermined recruitment sites (listed above in Section 4. “Selection and Enrollment of Participants”), we will also be recruiting from the community through posted flyers, newsletters, social media/online platforms, and the project website. We may not be aware of the specific treatment requirements or programming at all locations that potential participants may be receiving their buprenorphine treatment. Due to the varied nature of buprenorphine treatment at outpatient substance use clinics, it is unlikely that participants across sites will receive the same treatment experience. However, since all participants will currently be receiving buprenorphine for the treatment of an OUD through a provider’s prescription, we assume that participants will all be receiving the minimal standard of care dictated in the buprenorphine prescription guidelines (e.g regularly meeting with their prescribing physician in order to renew their prescription). The level of participant involvement with their buprenorphine provider (e.g. frequency of appointments, requirements for outside counseling in addition to buprenorphine treatment, requirements for providing drug screens, etc.) may vary from clinic to clinic, as will exposure to other forms of substance use treatment (e.g. relapse prevention) and/or 12-step principles to encourage abstinence and improve coping skills. We will

ask participants to provide information regarding treatment experiences during the baseline (enrollment) interview and at all follow-up assessments in order to control for any potential confounding factors during analyses. No efforts will be made to influence the prescribing practices of other providers and study therapists will be barred from discussing clinical information about participants with any treatment providers, except in cases in which reporting (ex. suicide, homicide, child abuse) is clinically necessary.

Information/data sharing with the participant's provider

Information regarding participant experiences, including experiences reported during the PPMI and EUC sessions and during data collection, will remain confidential and will not be shared with the participant's provider unless there is an immediate risk of harm to self or others, or the participant needs emergency medical attention. If a participant discloses information indicating acute risk to harm him/herself, we will enact our risk protocol, which may include contacting the participant's clinician, national suicide hotline, psychologist on call, etc. [See Section 7 "Safety Assessments" and the Data and Safety Monitoring Plan for additional information on Risk protocols].

Dr. Lin (PI of the project) is an Addiction Psychiatrist and a buprenorphine provider at the Ann Arbor VA Healthcare System. Dr. Lin's patients could potentially learn about and enroll into the RCT through project recruitment at the Ann Arbor VA. Referral to other psychotherapy options is often used by Dr. Lin in conjunction with medication treatment as part of the standard level of care provided to her patients. Therefore, if Dr. Lin would provide information regarding the study to patients, it would be made clear that this is part of standard practice, the intervention being provided in the study is experimental in nature, and that their participation in the study would not influence or affect the standard level of care they would receive from the VA. A statement disclosing this possible conflict will be included on the VA Informed Consent Form Document that will be provided to all VA research participants. Dr. Lin will not have access to identifiable information or data regarding participants recruited from the Ann Arbor VA. Any data, reports, or communications regarding participants will only include a unique Study ID number or be presented in aggregate form (whenever possible) and will aim to protect patient confidentiality. Providers approached to participate in the qualitative interviews for Specific Aim 4 will be approached by research staff and not Dr. Lin in order to lessen any possible coercion.

Dr. Ilgen (PI of the project) is the Director of the University of Michigan Addiction Treatment Services (UMATS), a recruitment clinic site for this project. As director, Dr. Ilgen oversees the operations of the clinic and the medical professionals providing services to patients. Dr. Ilgen, however, does not provide any clinical services to any UM patients, therefore, we do not anticipate any information/ data sharing issues to arise from this appointment. Data provided in reports and communications will also include a unique Study ID number or be presented in aggregate form. Providers approached to participate in the qualitative interviews for Specific Aim 4 will be approached by research staff and not Dr. Ilgen in order to lessen any possible coercion. Providers will be made aware that participation in qualitative interviews is voluntary and will not affect their position or work environment in any way.

Treatment contamination during the study.

Because patients assigned to both conditions may be treated at the same clinic location, it is possible that they may talk to one another and discuss their experiences in treatment, however it

is worth noting that the clinic locations selected see a large volume of patients and the number of participants in either condition at any given time will be a small minority of the total number of participants seen at the clinic locations. This decreases the chances that significant contamination will take place.

Ensuring careful fidelity to the PPMI and EUC session manuals (see details in the next section) will be particularly important given that each therapist will deliver both conditions. Since the same therapists will be trained to conduct both therapy sessions, there is a possibility of inadvertent contamination across conditions. With participant permission, all PPMI and EUC sessions will be audiotaped to ensure fidelity to the condition content. Delivering the condition sessions raises three possibilities related to contamination:

(1) Contamination of PPMI with elements of the EUC condition: The EUC condition will present educational information on buprenorphine treatment and pain management that is widely available in the community (i.e. pharmacy pamphlets, publicly available online tools and resources etc.). Thus, the discussion of this information with participants enrolled in the PPMI condition should not "contaminate" the PPMI condition with any information that would not normally be discussed in response to standard patient questions about pain or that is substantially different from what is often discussed in standard SUD treatment.

(2) Contamination of the EUC condition with elements of the PPMI treatment: This potential contamination is of greater concern when the same therapists are delivering both conditions. PPMI will be delivered by trained therapists in a systematized manner. If any contamination does occur, it is expected to be minimal. We will be monitoring the content of both groups and coding for fidelity to both the PPMI and EUC conditions throughout the duration of the trial. If participants in the EUC condition are exposed to content from the PPMI condition, this will be detected as part of the ongoing measurement of integrity of the EUC condition. Therapists responsible for the contamination will participate in re-training and will be re-evaluated to ensure further contamination or drift does not occur. We will also be assessing the presence of key components of the PPMI condition (self-efficacy, motivation, coping and acceptance) in all patients so that we would be able to detect if EUC participants report significant increases in these domains during the follow-up time period. For more information on fidelity monitoring, please see the section "Therapist Training and Study Fidelity Monitoring" below.

(3) Contamination of standard treatment at the study site with elements of either of the two conditions or information gathered during the conduction of the research project: Both conditions will be provided by members of the research team who are not affiliated with any recruitment clinics or responsible for direct patient care at any of the potential recruitment clinics. Thus, both the PPMI and EUC condition study therapists will not directly influence the standard course of buprenorphine, pain, or OUD treatment in these patients. Neither of the two conditions makes explicit or implicit recommendations about how the participants should change their overall approach to treatment course (i.e., length of stay, medication doses, etc.) at their clinic. In addition, as stated previously, information gained during the

condition sessions will not be communicated to the patient's treatment providers except in cases outlined in the limits of confidentiality. Information regarding medication adherence, continued substance use, or any other risky behaviors will not be directly communicated to any treatment providers in an effort to remain separate from their treatment. These topics will be discussed with the patient as part of the study sessions, and patients will be encouraged to share their experiences with their providers at their next appointments. In our prior experience, we have found that in interacting with clinics, although they are very welcoming of the research team the staff are very busy and the standard of care is not directly impacted by our presence.

Staff training and Study Fidelity Monitoring

For this project, all trainings will be directed by the Principal Investigators, and will be conducted by senior study staff, the clinical supervisors, and/or the project managers. A detailed training plan with milestones will be generated for the study therapists who will be providing both the PPMI and EUC conditions. For both conditions, training will involve an overview of the literature on OUD and buprenorphine as well as differing pain conditions and their treatment. Based on the knowledge level of the study therapists, additional trainings, seminars, or training tools may be assigned as needed to ensure that therapists are qualified and capable of discussing issues surrounding opioid use, chronic pain, and buprenorphine treatment with participants. Therapists will be asked to read relevant articles as well as all condition manuals in order to familiarize themselves with the session content. Therapist training may also include workshops provided by key investigators and consultants including but not limited to Drs. Ilgen and Lin. This training will involve a review of basic CBT principles, the rationale for the use of CBT to manage pain and reduce substance use, an overview of the use of buprenorphine treatment for OUDs, a review of theory and research, a detailed description of the intervention (including review of session outlines, handouts, and staff manual/instructions), audio-taped examples of intervention techniques (from the prior study in addiction treatment patients), and role playing. In light of findings that drift occurs most often in earlier stages of project implementation, the start-up period in which the study therapists are trained will be important to establishing the fidelity of both conditions. Therapists will be required to conduct several role plays that will be observed (either in person or via recording) by key clinical staff in order to determine whether or not the therapist is proficient at delivering the session content. Therapists will need to show at least a 70% adherence rate to session content to be considered proficient before they may begin to deliver the PPMI or EUC condition to participants. Likewise, therapists must score high enough on the competence measure in order to proceed to delivering the PPMI condition to participants. For more information on fidelity monitoring scales, please see the sections "PPMI and EUC Integrity and Fidelity monitoring" below. Therapy sessions with non-practice participants will be evaluated by key study staff under the following schedule:

(1) the first 8 sessions for each therapist will be assessed for protocol fidelity and the therapist will be provided comments and/or corrective feedback to ensure the above competence metrics are achieved; and
(2) three sessions for each therapist will be reviewed by a PI or Clinical Supervisor at random each month to ensure ongoing fidelity to the PPMI or EUC condition.

New role play scripts will be developed for portions of the intervention that are specific to buprenorphine retention as well as issues that may arise over the phone or video chat. We have many good training examples from our pilot study and previous work. Materials will be available for those therapists who are not able to attend the initial training or who are hired after any workshops have been completed. Since the material in the study sessions may focus on difficult issues, study therapists will also receive training on how to handle potential crisis situations and adverse events. In addition, the study therapists will receive ongoing supervision of recorded therapy sessions with clinical supervisors throughout the trial.

PPMI and EUC Integrity and Fidelity monitoring: With participant permission, all PPMI and EUC sessions will be audio recorded to ensure therapist fidelity to the condition materials. The development of the integrity measures will be based on procedures used in Project MATCH and the prior experience of our research group. For each session topic, dichotomous items for therapist adherence to session content will be generated from session outlines and materials to include specific session topics covered. This will produce eight Session-Specific Adherence Rating Scales per condition. To produce a Therapist Skill/Competence Scale for PPMI to apply across sessions, Likert items covering general CBT (e.g., delivery of session rationale in CBT framework, skill teaching, in session CBT exercises) therapist behaviors will be generated based on the Cognitive Therapy Rating Scale (CTRS). Instructions regarding item intent, examples and scoring guidelines will be developed for the Session-Specific Adherence Rating Scales, as well as the Therapist Skill/Competence Scale. A similar scale will be developed for the therapist skill/competence for EUC condition that focuses on non-specific therapeutic techniques (e.g. active listening, etc.) Approximately 25% of session recordings will be double-coded using the Adherence and Competence scales at the conclusion of the study to determine fidelity measurements. We have used similar procedures in prior intervention studies which have resulted in instruments with sound psychometric properties.

5.2 Handling of Study Conditions

Participants in both conditions will receive the study session content delivered by trained study therapists via telephone or video chat. Once the baseline assessment is completed and the participant has been randomized to the study condition, participants will be provided with the appropriate patient workbook or brochures and necessary information for participation in their assigned condition. Study therapists will explain the nature of the sessions to the participants and will answer any questions they may have regarding how the remaining sessions will be completed remotely. In addition, all participants who complete the first remotely delivered session in either condition (PPMI or ECU) will receive $40 to offset any potential costs that they might incur due to the use of their phones (minutes or data). It will be the responsibility of the study therapist assigned to the participant to set an appropriate therapy schedule (dates and times for therapy sessions) and to communicate that schedule and any changes to that schedule with the participant. In general, and where possible, study sessions should be scheduled at the beginning of treatment and should be set up on a consistent basis to encourage completion (e.g. scheduled Tuesday and Thursday at 2:00pm for the next 4 weeks). During the delivery of both conditions, study therapists will follow the therapy manual for each condition and if using video chat, the therapist may display the condition materials on the screen. All procedures (check-in forms, session activities, handouts, feedback forms, etc.) will be delivered for each session according to the manual guidelines. Deviations from delivering the approved session content -in the order intended- should be avoided unless the deviation is necessary for the safety and well-being of the participant (e.g. if a participant reports

acute, debilitating withdrawal symptoms at the beginning of the session, session content may be diverted until it is clear the participant is safe). Any session content or procedural deviations that occur during the therapy sessions will be communicated to the project managers and/or clinical supervisor for documentation in the trial record. Further details of completing study intervention accountability records will be provided in the study Manual of Operations (MOP).

5.3 Concomitant Interventions

The PPMI and EUC conditions are designed to augment current OUD treatment, not to take the place of current treatment. Therefore, due to the nature of the study sample (chronic pain patients with OUD on buprenorphine), it is expected that participants may be engaged in a variety of other treatments, either therapeutic or pharmacologic in nature, during the duration of the study. Participation in this study will not be restricted by any additional treatments they may be receiving.

5.3.1 Allowed Interventions

Participants may continue to take any prescribed medications including medications for physical health conditions, mental health conditions, or medications for the treatment of OUDs, including buprenorphine during their study participation. Participants may continue to take prescription opioid medications and/or other prescription medications for the treatment of a substance use disorder (e.g. disulfiram). Participants may be required by their treatment provider to participate in some form of outpatient counseling (including CBT treatment) or recovery self-help groups as a requirement of remaining on buprenorphine through the treatment clinic. Because remaining in buprenorphine treatment is the primary outcome in this study, involvement in these auxiliary treatments will be allowed. Data will be collected during all study assessments to capture the scope and frequency of the participant's involvement in additional treatment activities during their time on study. Participants may also be receiving medical care or treatment for a pain condition (e.g. physical therapy, acupuncture, etc.) while in the study. When possible, treatment records at the study sites will be reviewed to gather information regarding participant treatment involvement during the study. Where treatment records are not available or accessible through a signed release of information, participant self-report of treatment involvement collected at follow-up will be used to track treatment involvement.

5.3.2 Required Interventions

There are no required interventions a participant must engage in while in the study. Prior to enrollment in the study, participants must be actively participating in buprenorphine treatment for the treatment of an OUD. While actively taking the medication is a requirement for study enrollment, discontinuing buprenorphine treatment will not result in the termination of study participation.

5.3.3 Prohibited Interventions

There are no prohibited interventions associated with study participation.

5.4 Adherence Assessment

For this study, adherence to the study intervention condition (PPMI) will be defined as participation in at least 50% of the condition sessions. This would equate to participating in at least 4 of the 8 study sessions. The PPMI condition is designed to be progressive in nature, with each

session building on materials learned or discussed during previous sessions. Because of this, receiving at least 4 sessions of material in the PPMI condition related to chronic pain management and buprenorphine adherence/retention, will be considered an adequate dose. Likewise, adherence to the study control condition (EUC) will also be defined as participation in at least 50% of the condition sessions, or 1 of 2 study sessions. Due to the nature of the study (a behavioral therapy intervention study), participants will not be required to attend study sessions and will not be compensated for their involvement in the individual sessions. Study therapists and research staff will discuss the benefits of remaining engaged in the study treatment during the initial study meeting, however participants will be free to discontinue the study sessions at any time. Study therapists will make reasonable attempts to contact the participant should they disengage from the sessions. Participants will only be allowed to complete study sessions up to 6 weeks post enrollment. This cutoff was determined to allow for adequate time for the participant to complete the 1-month follow-up assessment. Participants will be eligible to participate in all follow-up assessments regardless of study session participation.

6. STUDY PROCEDURES

Below please find the study Schedule of Events. The eligibility screening survey is expected to take approximately 5 minutes to complete. We expect the initial enrollment assessment will take approximately 2 hours to complete, while the remaining follow-up assessments will take approximately 90 minutes to complete. This length is comparable to research assessments conducted by this research team in multiple projects. In these previous instances, patients were typically able to complete the entire assessment without problems. In the occasional case where a patient became tired or irritable, the assessment was split into two sessions and completed within the next couple of days. This technique was highly successful and did not result in problems with missing data. We will utilize this same strategy in this study and do not expect problems due to participant burden. We expect the weekly surveys will take approximately 5-10 minutes to complete.

6.1 Schedule of Evaluations

Assessment	Screening	Baseline, Enrollment, Randomization	PPMI or EUC Sessions: Treatment Visits	Weekly surveys	1-month follow-up	3-month follow-up	6-month follow-up	9-month follow-up	12-month follow-up
Electronic or Verbal Consent for eligibility screening	X								
Demographics – age, sex, recruitment location	X								
Self-reported pregnancy	X								
Access to telephone	X								
Numeric Rating Scale for Pain Intensity (NRS-I)	X			X	X	X	X	X	X
Buprenorphine treatment involvement	X	X		X	X	X	X	X	X
Rapid Opioid Dependence Screen (RODS)	X								
Inclusion/Exclusion Criteria	X	X							
Informed Consent		X							
The Structured Clinical Interview for DSM-5 Disorders: Substance Use Disorders Section, Opioids only (SCID-5)		X							
TimeLine Follow-Back (TLFB)		X			X	X	X	X	X
Legal Questions		X			X	X	X	X	X
Treatment Services Review		X			X	X	X	X	X
Urine Drug Screen		X			X	X	X	X	X

Assessment	Screening	Baseline, Enrollment, Randomization	PPMI or EUC Sessions: Treatment Visits	Weekly surveys	1-month follow-up	3-month follow-up	6-month follow-up	9-month follow-up	12-month follow-up
Enrollment/Randomization		X							
Demographics & Military History		X							
Veterans RAND 12 Item Health Survey (VR-12)		X			X	X	X	X	X
Barriers to Treatment		X			X	X	X	X	X
Buprenorphine Diversion		X			X	X	X	X	X
Beliefs about Buprenorphine treatment		X			X	X	X	X	X
Brief Pain Inventory – Short Form (BPI-SF)		X			X	X	X	X	X
Chronic Pain Acceptance Questionnaire (CPAQ)		X			X	X	X	X	X
Self-efficacy to Manage Chronic Conditions – Pain		X			X	X	X	X	X
Confidence Questionnaire		X		X	X	x	x	x	x
Patient Health Questionnaire (PHQ-9)		X			X	X	X	X	X
General Anxiety Disorder (GAD-2)		X			X	X	X	X	X
Alcohol Use Disorders Identification Test –Concise (AUDIT-C)		X			X	X	X	X	X
Injection drug use and overdose history		X			X	X	X	X	X
Social Support		X			X	X	X	X	X
Reasons for Leaving Treatment Questionnaire (RLTQ)					X	X	X	X	X
Symptoms and Behavior Questions				X					
Post-treatment survey (1 time)					X				

6.2 Description of Evaluations

In summary, participants will be assessed on the following schedule. First, they will complete an electronic or verbal consent prior to completing a brief eligibility survey for ("*Screening"*). Next, all eligible participants will provide a full study consent and complete the baseline research assessment. This includes a survey, a research staff administered interview, and a voluntary urine drug screen *("Baseline, Enrollment, Randomization").* Participants will be randomly assigned to receive either the PPMI or the EUC condition based on gender, past year use of heroin, and veteran status. Participants will then complete one of two conditions: PPMI, which involves 8 one-on-one therapy sessions conducted via phone or video chat over the course of 4-6 weeks *("PPMI Sessions: Treatment Visits");* or the EUC condition that will complete 2 educational sessions via phone or video chat over the course of 4-6 weeks ("*EUC Sessions: Treatment Visits")*. Follow-up assessments for both conditions will mirror the baseline assessment and will include a survey, a researcher administered interview, and a voluntary urine drug screen. These assessments will occur at 1-month (i.e., immediately following completion of the PPMI or EUC conditions*; ''1-month follow-up"*), 3-months *("3-month follow-up"*), 6-months, 9-months, and 12-months (i.e. study completion; *"12-month follow-up")* post enrollment. During the course of the study, research staff may access participant patient records at the treatment sites (with appropriate releases of information obtained from participants and treatment sites and IRB approval) for information on variables of interest or participant contact information (e.g. number of clinic visits, types of treatments engaged in, medications prescribed, results of urine toxicology tests, etc.). Study participation will be complete following the completion of the 12-month follow-up assessment.

Participant study compensation

- ***Baseline Assessment:*** Participants that consent to the RCT will be remunerated $50 for completing the baseline enrollment assessment.
- ***Phone Compensation (PPMI and EUC sessions):*** Participants will be asked to complete 8 therapy sessions for PPMI condition or 2 sessions for EUC conditions via telephone or video chat. To lessen the burden of these sessions on participants, upon completion of the first phone session for each condition, all participants will receive $40 to offset any potential costs that they might incur due to the use of their phones. This phone related payment is not contingent upon treatment participation and will be given to all participants who attend at least one phone session of their assigned condition.
- ***Weekly Check-in Surveys:*** Participants will be asked to complete a brief survey each week for the first 13 weeks they are enrolled in the study. These surveys will ask about key variables of interest (e.g. pain, substance use, and buprenorphine adherence) and will allow participant to report on outcomes close in time to experience. The surveys can be completed via phone or online. For each survey completed, the participant will receive $10. If a participant completes all 13 weekly surveys, they will receive an additional $10 payment. Total potential compensation is $140 ($10 x 13 weeks on study= $130 + $10 for completing all surveys).
- ***Follow-Up Visits:*** Participants will be remunerated $40 for the 1-, 3-, 6-, and 9-month follow-ups and $50 for the 12-month follow-up. Total potential follow-up incentive is $210.
- ***Urine Samples:*** At the baseline, 1-, 3-, 6-, 9-, and 12-month follow-ups, participants will be asked to provide a voluntary urine sample for a drug screen. Participants who provide a sample will be compensation with $10 at each assessment. Total potential urine sample incentive is $60.

Total potential compensation for participating in the entire study is $500. All compensation will be given in the form of gift cards. Small items of insignificant value such as pop, water, water bottles, card holders, pens, magnets, etc. may be given to participants during the study and will not be used as a contingency of study participation.

The chart below provides a summary of study activities with their approximate length, payment amount, and main method of interaction.

Time Period	Approximate length	Payment Amount	Main Interaction Type
Eligibility Screening	5 minutes	n/a	In-person / Phone / Online
Enrollment (Baseline) Assessment	2 hours	$50 (+ $10 for urine sample)	In-person / Phone / Online
PPMI condition (8 sessions)	1 hour each (8 hours total)	$40 for phone use	Phone
EUC condition (2 sessions)	5-10 minutes each (10-20 minutes total)	$40 for phone use	Phone
Weekly Surveys (13 total)	5 minutes each (65 minutes total)	$10 each (+ $10 for completing all)	Phone / Online
1-month follow up	1.5 hours	$40 (+ $10 for urine sample)	In-person / Phone / Online
3-month follow up	1.5 hours	$40 (+ $10 for urine sample)	In-person / Phone / Online
6-month follow up	1.5 hours	$40 (+ $10 for urine sample)	In-person / Phone / Online
9-month follow up	1.5 hours	$40 (+ $10 for urine sample)	In-person / Phone / Online
12-month follow up	1.5 hours	$50 (+ $10 for urine sample)	In-person / Phone / Online
	Total	$500	

6.2.1 Screening Evaluation

Potential participants will be recruited to participate in the eligibility screening in a variety of ways. For details, please refer to Section 4 “Selection and Enrollment of Participant” above, specifically subsection 4.3 “Study Enrollment Procedures”. Results of all record reviews, in-person, online, and phone recruitment outcomes will be documented in the Screening Eligibility Log.

Consenting Procedure

A general description of the consent process is described above in Section 4.3 “Study Enrollment Procedures”. In summary, this study will have a two consent process in which consent will be obtained prior to the completion of the eligibility screening, and a second consent will be obtained from participants prior to their enrollment into the full RCT. Trained research staff will conduct the informed consent processes. For this study, the informed consent process may be conducted by a study project manager, the research

assistants, or the study therapists. All research staff will have received training by the investigators, project managers, and/or the IRB coordinator regarding the consenting process. Trainings may include but are not limited to: attending specialized trainings regarding informed consent in research, role plays, quizzes, and handouts regarding the informed consent process. Training topics will include going over the components necessary in consenting, the voluntary nature of the study, importance of properly consenting individuals, rights of participants to withdraw from the study, etc.

Before a potential participant completes the eligibility screening survey to determine initial study eligibility, electronic or verbal consent will be obtained. A request for a waiver of documentation of informed consent has been requested from the IRB for this eligibility screening process. For those participants who are eligible and agree to participate in the full RCT, full informed consent will be obtained before the participant engages in further study activities. Before moving onto the eligibility screening survey, participants will have the ability to print, save a copy of the electronic consent information sheet, or be provided a paper copy if requested. Those who complete the eligibility survey via phone may have the consent information sheet mailed or e-mailed to them if requested.

For those participants who meet initial eligibility requirements for the RCT portion of the study, research staff will inform them of their eligibility and give more details about the study (either in-person at the recruitment appointment or via phone/e-mail for those who complete the eligibility survey online through the project website). The participant and research staff will choose an appropriate time to complete the RCT study enrollment process (i.e. the consent form, baseline assessment, initial condition meeting, etc.). At that time, individuals interested in participating in the study will review the consent with the research staff prior to beginning any study activities. During this process, patients will be informed of the general nature of the study, what their involvement entails, the risk/benefits, and limitations to confidentiality. As part of the informed consent process, patients will be told that participation is voluntary, that they can withdraw at any time, and that this will not impact their treatment. In addition, participants will be provided information about randomization, intervention conditions including audio recording, compensation for study activities, and baseline and follow-up assessment requirements. The limits of the NIH Certificate of Confidentiality will be explained in the consent form, but study staff will also verbally explain the limits of confidentiality. After reviewing the consent form with the patients, research staff will ask the patient if he/she has any questions regarding their participation or the study requirements and limitations. Any patients who are not interested will be thanked for their time. Any patients who request more time to review the consent form or consult with others will have the opportunity to do so. These patients will be contacted by research staff at a later time or will be able to contact research staff themselves. Those interested in participating will be asked to provide written or verbal informed consent. When providing written informed consent, participants will be given a signed copy of the consent form to keep for their records. For those providing verbal consent, study staff will record that verbal consent was obtained. If a participant was not able to receive an electronic copy of the consent to have on hand to review during the phone consent process, they will be sent a copy by mail or email after consent is received. Study staff will review the consent form for accuracy and completeness before proceeding with the baseline enrollment assessment and randomization. Once informed consent has been obtained, the research staff will proceed with the baseline assessment (please see

Section 6.1 “Schedule of Events” for a list of specific measures and tasks). Documentation of the informed consent will be entered into study tracking logs and appropriate case report forms will be completed.

Since informed consent is an ongoing process, should the study protocol be amended in a way that may impact study participation, participants may be required by the IRB to provide consent again to continue participation. All changes to the consent forms will be approved by UM IRBMED and VA Ann Arbor IRB and any additional entities necessary prior to re-consenting of any participants. When an in-person baseline assessment is conducted, there may be temporary transportation of paper informed consent forms, paper data collection instruments, and other paper administrative forms (e.g. case report forms, Locator forms, payment receipts, etc.) from treatment clinics and/or community locations where data is collected to the research offices. Paper forms will be transported through the use of a lockable carrying cases and kept with study staff at all times. Because consent forms, locator forms, and payment receipts will contain identifying information, they will be kept in locked file cabinets in research offices. These file cabinets will be separate from study data. All electronic consent forms will be stored on a secure server. Research records, including consent forms, and/or identifiers will be retained in accordance with the NIH Records Management Schedule.

Screening

Participants will complete an electronic and/or verbal consent, depending on recruitment type (See Section 4.3 “Study Enrollment Procedures” above), prior to answering eligibility questions. The eligibility screening will involve the collection of data through survey questions (please Section 6.1 “Schedule of Events” for specific measures) and should take approximately 5 minutes to complete. Survey questions related to the inclusion/exclusion criteria will be asked in the following order:

- Basic demographic information (age, biological sex, gender, state and country residency)
- Self-reported pregnancy (*dichotomous yes/no question*)
- Recruitment location *(multiple response options)*
- Accessibility of telephone (*dichotomous yes/no questions)*
- Average pain score within the past 3 months (*measured by the NRS-I*).
    - The Numeric Rating Scale of pain intensity (NRS-I) is an 11-point numeric rating scale (0 = no pain, 10 = worst pain imaginable) widely used in medical settings to assess global pain intensity.
- Current buprenorphine prescription (*multiple response options)*
- Route of administration for buprenorphine medication (*multiple response options*)
- Opioid use disorder diagnostic screen (*measured by the RODS*).
    - The Rapid Opioid Dependence Screen (RODS) is an 8-item measure designed to screen for opioid dependence.

Once the participant completes the eligibility survey, responses will be reviewed to assess for potential eligibility. For those participants who are ineligible, their participation in the study will be complete at this time. No identifiable information or contact information

will be collected from those participants who screen ineligible, or from those participants who screen eligible but report no interest in continuing on with the research study. All eligibility criteria will be confirmed, including most recent buprenorphine treatment episode start date and self-reported use of prescribed buprenorphine within 10 days of the enrollment interview, with the participant prior to the participant being enrolled in the study. Participants will have 60 days from the date the eligibility screening is completed to schedule and complete the baseline enrollment assessment. Eligible participants who do not complete enrollment within that time frame will be considered to have declined to participate in the full RCT.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

Participants will be considered enrolled into this study *("Baseline, Enrollment, Randomization")* once they have completed the informed consent process as described above, eligibility has been confirmed, and the participant has been randomized. Participants who were initially eligible based on the eligibility screening but become ineligible based on most recent buprenorphine treatment episode start date, report of prescribed buprenorphine medication use within the 10 days prior to the enrollment interview, or the OUD diagnostic interview administered during the baseline assessment (or another reason) will not be randomized. Therefore, they will not be considered enrolled in the trial and will not be counted in the final study. Enrollment and Randomization date will be captured in study tracking logs and study records, including case report forms. All participants enrolled in the study will be included in subsequent data analyses.

Baseline Assessments

Following the consent process, participants will complete the baseline assessment *("Baseline, Enrollment, Randomization"*). The baseline assessment will take approximately 2 hours to complete and participants will be remunerated up to $60 for their participation ($50 for baseline assessment + $10 for voluntary urine sample). Because we will need to contact participants for follow-up assessments, the research staff member will collect detailed contact information using the Locator Form during this assessment. This information will include the participant's phone number(s), address(es), e-mail address(es) and contact information for family members/friends who would know how to reach them. Participants will be asked to complete a survey during the enrollment assessment either with a research staff member (via researcher / study therapist administered interviews in-person or by phone or video chat) or use self-report surveys (completed electronically via tablet or emailed survey link or in a paper version if preferred by the participant) to gather data to assess additional demographics, pain and functioning, substance use, and use of buprenorphine. The baseline assessment will also include a researcher administered interview, delivered in-person, by phone, or video chat, containing the Time Line Follow Back (TLFB) assessment, which is designed to assess for opioid and other substance use over a given time period. Information regarding buprenorphine treatment and recent medication usage will also be collected via the TLFB and will be used to confirm study eligibility. In addition, participants will be given a researcher administered diagnostic interview (Structured Clinical Interview for DSM-5; SCID-5), delivered in-person, by phone, or video chat to confirm the presence and severity of an Opioid Use Disorder (OUD) diagnosis within

the past 12 months. This interview will be administered at the beginning of the assessment to confirm study eligibility. Any participant who does not meet criteria for an OUD based on the diagnostic interview will be informed they are not eligible for the full study and will be thanked for their time. These participants will not continue with the full baseline enrollment assessment, will not be randomized, or considered enrolled into the trial, and their participation will be considered complete at that time. Participants who do not meet full eligibility during the baseline enrollment assessment will still receive study payment for their time. The majority of instruments have been used widely and evaluated for their appropriateness with all participants (including women and minority groups) will ask about the following topics of interest:

- **Demographic information** will be collected to assess basic demographic characteristics such as age, gender, educational background, employment, income, ethnicity, and marital history. Additional information regarding **Military history and involvement** will also be collected.
- **Overall functioning.** The Short Form-12, Veteran's Version (VR-12) will measure physical and emotional role functioning. This brief measure provides broad indicators of level of functioning in terms of physical and emotional health. Because the VR-12 is frequently used in research in a variety of health care settings, the scores in these domains can be readily compared to samples from other SUD and other treatment settings.
- **Buprenorphine Treatment Experiences and Barriers to Treatment** such as information related to length of treatment, treatment conditions, and confidence questions were developed for this study by the study team.
- **Buprenorphine Diversion** will be measured using a modified version of the prescription medication diversion questions initially developed as part of the Student Life Survey (SLS).
- **Beliefs about Buprenorphine Treatment** will be assessed using a modified version of the Patient's beliefs about Medication scale developed by Uebelacker et al. (2016) which collects information on efficacy, safety, and consistency with being drug-free related to buprenorphine treatment.
- **Intensity of pain:** In addition to the NRS-I listed above, The Brief Pain Inventory –Short Form Version (BPI), a widely used, validated measure of pain experience, will also be used (Gjeilo, Stenseth, Wahba, Lydersen, & Klepstad, 2007).
- **Pain Acceptance.** The Chronic Pain Acceptance Questionnaire (CPAQ) will be completed at the baseline and all follow-up assessments. The revised scoring of this measure will be used to measure the willingness to engage in activities when pain is present and the extent to which participants are willing to have pain present without trying to avoid or reduce pain. The CPAQ (alpha = .78) is comprised of four sub-scales that measure activity engagement (alpha = .82), pain willingness (alpha = .78), thought control (alpha = .64), and chronicity (alpha = .62).
- **Self-efficacy – Pain management** will be measures using the PROMIS item bank related to Self-Efficacy for Managing Chronic Conditions- Managing Pain and Managing Emotions. Multiple scales will be used to assess a participant's level of coping with pain management and emotions that come with chronic pain. Additional questions have been drafted by the study team regarding confidence to manage pain in the future in different situations.

- **Depression**. Patient Health Questionnaire (PHQ-9). The PHQ-9 will be used to assess current symptoms of depression. This 9-item, patient self-report tool yields total scores ranging from 0 to 27 and was developed for use in healthcare settings. The PHQ-9 has acceptable reliability, validity, sensitivity, and specificity (PHQ-9 score ≥ 10 has a sensitivity of 88% and a specificity of 88% for major depressive disorder), quantifies depression severity, and is sensitive to change.
- **Anxiety.** The Generalized Anxiety Disorder 2-itme scale (GAD-2) will be used to assess symptoms and severity of anxiety. The GAD-2 is an empirically validated tool for screening for anxiety disorders in clinical settings (Kroenke, et al., 2007).
- **Opioid Use Disorder Diagnosis.** The Structured Clinical Interview for DSM-5 Disorders: Substance Use Disorders Section (SCID-5) will be used to assess eligibility based on an OUD diagnosis in the last 12 months. The SCID is an empirically validated measure which assesses criteria for DSM-5 diagnosis of a substance use disorder. The SCID has been shown to have internal consistency of alpha = .80 (Shankman, et al., 2017). Only questions related to opioid use disorders will be administered.
- **Alcohol, Drug, and Buprenorphine Use**: These items will be measured via self-report as well as via researcher administered interview. During the interview, the Time Line Follow Back Interview (TLFB) will be used to assess the quantity and frequency of drinking and other drug use over a specified period of time. The TLFB is a calendar-assisted structured interview that provides the participant with temporal cues to increase the accuracy of recall. Participants are asked to recall how much they drank or used any other controlled substances on each day during the specified period of time (e.g. past 6 months, since last interview), starting with the most recent day and progressing back one day at a time. Percent days abstinent from alcohol and drugs will be used as the primary measure of substance use at each assessment time point. The interviewer-administered instrument has demonstrated test-retest reliability of greater than .86. Also, as part of the TLFB, participant swill be asked to report all days during the assessment time period which were spent in a controlled environment. For alcohol use specifically, the Alcohol Use Disorders Identification Test- Concise (AUDIT-C) will be used to measure alcohol consumption. This brief measure is widely used to identify at-risk drinkers and has sound psychometric properties.
- **History of Injection drug use and overdose.** One item from the High Risk Behaviors Survey (HRBS) will assess injection drug use in the past month. Additionally, overdose history will be assessed using items from the Overdose Experiences with Drugs scale. Additional overdose risk questions such as access to Narcan will also be asked.
- **Social Support.** Participants will be asked to complete a brief measure assessing perceived social support, with a focus on those who provide emotional and information support in the participant's lives. This measure was adapted from the National Institute of Health's Toolbox.
- **Legal Status.** Questions related to current and past and current legal issues will be modified from the Addiction Severity Index (ASI).
- **Treatment Service utilization**. In order to obtain data about treatment utilization, past six-month history of treatment (for drugs and/or alcohol and mental health) will be obtained at the baseline interview with items adapted from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) and used in prior work. This instrument elicits information about formal specialty substance use and mental health treatment services (both inpatient and outpatient), primary care brief interventions, and

self-help groups. These questions will be modified and repeated at subsequent follow-up to cover the interval of time since last interview.

- **Medical record abstraction (*Where applicable and allowable by the individual sites)*** Participant electronic medical records may be accessed by research study staff to collect information regarding buprenorphine treatment involvement. HIPAA authorization may be included in Part 2 (site information) of the informed consent or participants may be asked to sign a release of information if applicable.

Participants will also be asked to provide a voluntary urine sample for the baseline assessment and all follow-up assessments (i.e. 1-, 3-, 6-, 9-, and 12-months post enrollment) to analyze for recent substance and medication use. For each sample provided, the participant will receive an additional $10 payment (total possible study compensation for urine samples is $60). Our study team has experience collecting urine drug screens from several previous studies, and we have learned techniques for maintaining participant confidentiality during this process (e.g., providing participants with a bag for transporting the screening cup, checking the screen in a private location). When unable to complete an assessment in-person, participants will have the option to complete a urine drug test at home. Research staff will mail the urine sample cup with instructions on how to complete the test and submit a photo of the results to the research team via a link for upload or report results over the phone. We will be using the CLIA Waived UScreen Drugs of Abuse Cup with Adulterants to collect the urine specimen for testing. The test cups can detect up to 12 illicit and prescription drugs in one testing with up to a 99% accuracy rate. The model used in this study also has a built-in temperature strip.

This model will test for the following substances:

Drug Name	Abbreviation	Cutoff	Minimum Detection Time in Urine*	Maximum Detection Time in Urine*
Amphetamine	AMP	1000 ng/ml	2-7 hours	2-4 days
Barbiturates	BAR	300 ng/ml	2-4 hours	1-3 weeks
Benzodiazepines	BZO	300 ng/ml	2-7 hours	1-4 days
Buprenorphine	BUP	10 ng/ml	2-7 hours	2-3 days
Cocaine	COC	300 ng/ml	1-4 hours	2-4 days
Ecstasy	MDMA	500 ng/ml	2-7 hours	2-4 days
Marijuana	THC	50 ng/ml	2 hours	up to 5+ days
Methadone	MTD	300 ng/ml	3-8 hours	1-3 days
Methamphetamine	mAMP	1000 ng/ml	2-7 hours	2-4 days
Morphine/ Opiates	MOP (OPI-300)	300 ng/ml	2 hours	2-3 days
Oxycodone	OXY	100 ng/ml	1-3 hours	1-2 days
Phencyclidine	PCP	25 ng/ml	4-6 hours	7-14 days
Tricyclic Antidepressants	TCA	1000 ng/ml	8-12 hours	2-7 days

* Detection times listed are not guaranteed by test manufacturer.

Urine collection procedures

Specimens will be collected in a specimen container (test cup) about 4 oz. in size, although only a minimal amount of urine is necessary for testing. We will be using urine

testing kits that provide immediate results; therefore, the tests will be self-administered at the assessment location or by a participant in their home and results will be read and recorded by the research staff in-person or through receiving a photo of the completed test from a participant via a survey link or the participant will read the results to research staff via phone. No labeling or storage of the sample will be necessary, and no identifying information will be marked on the sampling container. The research staff member will provide the testing cup in person or by mail to the participant to use to collect their sample. Once sample collection is complete, the participant will be asked to close the cup using the cap provided. The participant will return the sample to the research assistant or place it on their counter until results are ready. The testing cup is self-contained; therefore, the research staff member or participant will not need to open the container for testing. Test results will be displayed on the test cup 5 minutes following the collection of the sample and results remain stable for 60 minutes. If conducted at home, the participant will take a clear, visible photo of the results panel with the date and time indicating when the test was done, or the participant will communicate the results to the staff member via phone. The photo will be uploaded using a link and will be sent to the study team. Results for the adulteration review are available by visually comparing the color of the reagent pads on the outside of the cup to the corresponding color blocks on the Color Chart at 3 to 5 minutes. Results for substance use will be interpreted in the following ways:

- **NEGATIVE** result: Two colored bands appear on the membrane. One band appears in the control region (C) and another band appears in the test region (T). Certain lines may appear lighter or thinner than other lines. A line is to be considered a line whether it is faint, light or dark.
- **PRELIMINARY POSTIVE** result: Only one colored band appears, in the control region (C). No apparent colored band appears in the test region (T).
- **INVALID** result: Control band fails to appear. Results from any test which has not produced a control band at the specific read time will be discarded. With participant permission, the procedure may be repeated with a new test.

The test cup also provides a test for adulteration of the sample. The test manufacture provides the following information regarding adulteration on their website: “Urine sample adulteration is usually achieved by substitution, dilution or the addition of adulterants including so-called ‘masking agents’ sold commercially. The use of adulterants can cause false negative results in drug tests by either interfering with the test and/or destroying drugs present in the urine. Dilution may also be used in an attempt to produce false negative drug test results. The Drug Tests In Bulk Pre Screen Plus Test (CLIA Waived) adulteration test is based on the color response of chemical indicators in the presence of adulterants. The following adulterants will be tested for this study:

pH: The pH determination of urine samples is based on the color change of an indicator in an acidic or basic medium. Normal urine pH ranges from 4 to 9. Values outside of this range may indicate the sample has been altered.

Specific Gravity: The specific gravity test is based on the pKa change of certain pretreated polyelectrolytes in relation to the ionic concentration. In the presence of an indicator, the colors change from dark blue to blue-green in urine of low ionic concentration to green and yellow- green in urine of higher ionic concentration. The normal range for

specific gravity is from 1.003 to 1.030. Values outside this range generally indicate specimen dilution or adulteration.

Oxidants/PCC (Pyridinium Chlorochromate): Bleach, hydrogen peroxide, pyridinium chlorochromate or other oxidizing agents react with an oxidant indicator to form a color complex. A blue-green, brown, or orange color indicates adulteration with bleach or other oxidizing agents. Normal human urine should not contain oxidants."

Following the recording of results, the urine sample will be discarded by flushing it down the toilet. This test provides only a preliminary analytical test result and will not be used for confirmatory analyses. During the consent process, participants will be informed that the results of urine tests will be kept confidential and will not be entered into their medical record or shared with any of the treatment staff at the treatment sites or with outside authorities (e.g. law enforcement). Product inserts for the test cups are included in the appendix for reference.

Randomization

Following completion of all data collection during the baseline assessment, participants will be randomized to a treatment condition – Psychosocial Pain Management Intervention (PPMI; n=100) or Enhanced Usual Care (EUC; n=100). Randomization to condition will be carried out blocking on gender (biological sex; male versus female), past year use of heroin (yes/no), and veteran status (community/veteran). Participant responses to questions based on biological sex and opioid use history obtained during the eligibility screening survey will be utilized to select the appropriate block for randomization. Research staff will confirm the participant responses before beginning the randomization procedures. "Gender" for randomization purposes will be operationalized as the biological sex the participant indicated they were assigned at birth. Additional questions regarding the gender the participant identifies with will also be collected but will not be used for randomization purposes. Should a participant decline to answer a key blocking variable during the survey administration, research staff will verbally ask clarification questions to determine block assignment. If a participant refuses to provide the necessary information that allows for the possibility of blocking, they will be excluded from participating further in the study.

Computerized randomization will occur in blocks of randomly chosen sizes in order to equalize randomization over time and to prevent the possibility that staff could unwittingly manipulate subject assignment to conditions. The study biostatistician will complete the treatment allocation sequence process prior to the start of recruitment for the study. Staff members who will be involved in the enrollment process will not be included in the randomization sequencing process. To further avoid manipulation of condition, randomization will not be determined until after all baseline data collection activities have been completed. We will utilize allocation concealment procedures to ensure that that research staff member enrolling the participant will not know in advance which treatment the next person will receive.

Once generated, documents that include the randomization sequence will be password protected to avoid inadvertent access by research staff involved in the enrollment process. Research staff will contact the project managers to randomize all participants using the randomization sequence provided by the biostatistician. The randomization process will be overseen by the project managers who will be notifying the research therapists of assigned

condition for specific participants at the completion of all baseline assessments. Randomization will occur once the baseline enrollment assessments are complete, which will take place no later than 60 days following the completion of the eligibility screening survey. Initiation of the study treatment condition (either PPMI or EUC) will occur immediately following randomization, when possible. Study sessions delivered via telephone or video chat should take place within one week of study enrollment and randomization for those in the PPMI condition and within two weeks of study enrollment and randomization for those in the EUC condition in order to provide enough time for all sessions to be completed within the 4-6-week treatment window.

6.2.3 Blinding

For this study, participants will not be blind to the condition they are receiving given the fact that the PPMI condition and the EUC condition are of varying lengths (8 sessions vs. 2 sessions). Despite this, we are confident that the nature of the EUC condition (e.g. a study therapist providing education and support to those with chronic pain engaged in OUD treatment) will produce enough of a supportive effect to provide a strong test of the added benefits of PPMI above and beyond the care typically delivered in the community. Study therapists who deliver the condition will not be blind due to the fact that they will be delivering both conditions. Therapists will, however, be trained and instructed to provide a similar level of attention to each participant during the session, regardless of treatment condition.

Data collectors responsible for the collection of follow-up data (post-enrollment data) (i.e. research assistants, project managers, or other study staff) will remain blind to the treatment condition assignment to ensure accurate and unbiased collection of trial outcomes. It is important to note that the primary outcome of interest (retention on buprenorphine treatment over 3-months post enrollment) will be collected via participant self-report through weekly surveys. Therefore, study staff will not be directly involved in the collection of those outcome data. Longitudinal data of the primary outcome (retention on buprenorphine treatment over 12-months post enrollment) will be collected by research study staff via researcher administered interview, and therefore these study staff will remain blind to the assigned treatment condition. In the event that longitudinal data may need to be reviewed for accuracy and coding following collection through case consultation meetings, outcome adjudicators, including investigators or project consultants will be blind to condition assignment to ensure unbiased coding of data. Importantly, the data managers and data analysts will remain blind to study condition when conducting all analyses.

6.2.4 Follow-up Visits

Participants will be asked to complete several different activities following randomization and condition delivery and are described in detail below.

Post-treatment survey. This survey will ask general questions about their experiences with both the study therapist (therapeutic alliance) and the session content. We have used similar measures tapping such constructs in prior research. This survey will be used as a supervision training tool for the therapists and research staff and as data for future intervention refinement purposes. In order to ensure participant privacy and encourage honest responses, research study therapists will not have access to the data collected via

the post-treatment surveys. The survey will be given once at the participant's first follow-up after completion of treatment sessions.

Session Attendance. Attendance of the condition sessions will be monitored to determine whether participants will utilize these therapies. Attendance will be tracked utilizing the Session Contact Form by each research study therapist or research staff at each session and attendance records will be consolidated to determine number of consecutive weeks in which sessions were attended and the total number of sessions attended by each participant.

Weekly Surveys. Following completion of the baseline (enrollment) assessment, participants will be asked to complete a survey once a week for the next 13 weeks (i.e. a total of 3-months post enrollment). These surveys will ask questions regarding pain level, pain functioning, buprenorphine treatment engagement, substance use, and some general questions about health and well-being and should take approximately 5-10 minutes to complete. Participants may be sent an e-mail from REDCap once per week asking them to complete the brief survey. The e-mail will contain a link to the REDCap platform where the participants may complete the survey. Participants will have 6 days from the time the e-mail is sent to complete the survey via REDCap. Participants may receive a system generated or study specific reminder e-mail to complete the survey before the link expires. Participants will not be allowed to complete a previous week's survey once a new link has been sent. This process will be repeated each week for the first 13 weeks of the study. Participants also have the option to complete the surveys over the phone. Research assistants will read the survey questions and record the participants answers in the REDCap survey. Following the completion of each weekly survey, participants will receive $10 or $130 for all 13 weeks. If a participant completes all 13 weekly surveys, they can earn an additional $10 payment, for a possible total possible compensation of $140 if all weekly surveys are completed.

Study Follow-up Time points. Full study follow-up assessments will be conducted at 1-, 3-, 6-, 9-, and 12-months post study enrollment and will utilize a combination of measures from the eligibility screening survey and baseline assessments (see Section 6.1 "Schedule of Events" for specific measures). These follow-up visits will be completed in-person, whenever possible, by phone, by video chat, or by email. Assessments are expected to take approximately 90 minutes each. Participants will have the option to complete a voluntary urine test at all follow up time points. The urine drug screening may be conducted in-person or at home by mailing the test kit to the participant. At each of the 1-, 3-, 6-, and 9-month follow-up assessments, participants will receive $40 for completing the assessment, with an additional $10 possible if they provide a urine sample for testing. Participants will receive $50 at the 12-month follow-up for completing the assessment, with an additional $10 for a urine sample. Participants who complete all study follow-up assessments could be compensated up to $260 total.

Follow-up assessments will take place in-person at the treatment clinic or another location of convenience in the community (e.g., participant's homes, ED, library, fast food restaurants) whenever possible, however assessments may also take place (1) online via REDCap survey, (2) over the phone, (3) over video chat, or (4) through a mailed paper survey where participants can complete surveys on their own and send back to research staff with a follow-up phone interview to complete the assessment. If follow-up assessments are

completed in-person outside of a study location, we will typically arrange for at least two research staff members to go together for safety reasons. All research staff will be required to follow study check-in procedures when conducting follow-up assessments. When meeting participants in public locations for assessments efforts will be made to ensure that others cannot overhear conversation between the participant and study staff, including maintaining sufficient physical distance with others and choosing locations that are not too crowded or busy. Percent of urines positive for substances and buprenorphine at each follow-up will be used to validate self-report measures of abstinence from substances and buprenorphine retention, however these tests will not be utilized as primary outcome data. We have extensive experience using similar methods in our prior work and previous research has shown that the validity of self-report of illegal drug use may be increased when a urine drug screen is also performed.

In order to ensure an adequate completion rate for the post-treatment follow-ups, we will use a series of strategies to locate participants that have been used successfully in our previous research. Using similar strategies, we typically achieve 12-month follow-up retention rates of over 80%. These strategies include utilizing a multi-faceted contact approach which includes contacting participant by mail, phone, in-person, and electronically where permitted, providing participants with reminder phone calls before appointments, and encouraging continuity of contact with individuals on the research team. As part of retention strategies, research staff will be trained in the importance of rapport-building with participants and professional boundaries. The research staff will contact the participants using the contact information provided at the baseline assessment for all follow-up contacts. In addition to participant's contact information, we will be asking participants to designate at least two contact persons who will be aware of their whereabouts should they become unreachable. Participants may be contacted via e-mail for study related correspondence, such as scheduling appointments or to complete surveys.

Research staff will also utilize publicly available websites (i.e. Google, whitepages.com, etc.) to obtain current contact information. Subjects may also be sent greeting cards on holidays and birthdays in an effort to increase participant retention. Subjects may also receive a certificate of recognition at the end of their assigned condition's sessions and/or at the end of the study. The certificate will congratulate the participant (include their name) for completing the appropriate part of the study. We may also include a business card for official study use, such as when meeting or sending correspondence to participants. A study official business card will include study information such as affiliation, study name, contact information, and/or individual study staff names.

Individuals identified as participant contacts will be contacted via phone or mail only when we are unable to reach the participant. Research staff will inform the contact that we are calling from the University of Michigan, or local site as necessary, and that the participant indicated we could contact them in cases in which we had trouble reaching the participant. Research staff will ask the contact person if they have any updated contact information for the participant or if they would pass along a message to the participant on our behalf. Information regarding the nature of the research project will not be shared with the contact person to maintain the confidentiality of the participant. Because this study will be based within treatment clinics, we will also utilize the electronic medical record systems (e.g. MiChart, CPRS) when allowable to monitor patient appointments and to gather contact information. Participants will be asked to sign a HIPAA authorization and/or a release of

information that allows the research team the necessary information. In our past work, we have found that this is a useful way to track changes in patient contact information and to identify good times to make contact with the patient.

Participants will be considered in the study following enrollment and randomization until the completion of the 12-month follow-up or end of the 12-month follow-up window, whichever comes first. Participants will have a total of 6 weeks to complete all study treatment condition sessions. Ideally, condition sessions will be completed by Week 5 of study participation to allow for the timely collection of 1-month data. 1-, 3-, 6-, 9-, and 12-month follow-up data may be collected from the follow-up visit due date ± 12 weeks (3-months).

6.2.5 Completion/Final Evaluation

A participant will be considered to have completed the study following the completion of the 12-month follow-up, or the determination that the participant has been "lost to follow-up". For the RCT, participants will be considered lost to follow-up following NCCIH guidelines. Specifically, for this trial, a participant will be considered lost to follow-up according to the following guidelines:

(1) A participant does not complete three consecutive study follow-up assessments **and** is unresponsive to study contact. "Unresponsive to study contact" will be defined as the inability of research staff to receive any response initiated from the participant by contact either (a) in-person (at an assessment or home visit), (b) through the telephone (e.g. phone calls), (c) through project correspondence (mail, e-mail, or text message) or (d) through completion of online follow-up surveys for a consecutive 6 months of study participation. Due to the nature of the study population (participants experiencing chronic pain and opioid use disorders) and the design of the study, it is expected that schedule deviations may occur over the course of a participant's enrollment in the study (e.g. participants may miss a scheduled study visit or therapy session). We will not consider these incidents of minor protocol deviations to be "lost to follow-up" until the participant has become unresponsive according to the above definition.

(2) A participant is no longer participating in study activities. For this project, this can occur by:

(a) a participant requesting to withdraw their participation from the study, either by verbally communicating this information to a research staff member or through written communication (e.g. e-mail, mail, or text message) from the participant received by a research staff member. Once this request has been received, the participant will no longer be contacted by study staff and their participation in the study will be considered complete. Participant data collected prior to the participant's decision to withdraw from the study will be used in data analyses unless the participant has specifically requested their data be removed; or

(b) a participant timing out of the study completion window. For this project, participants will be able to complete the final 12-month study

assessment from the assessment due date up until 3 months following that date. For example, if a participant is due to complete their 12-month follow-up on March 1, 2020 they will be eligible to complete that follow-up until June 1, 2020. On June 2, 2020 the participant will be outside of the study completion window and their participation will be considered complete.

Research staff may choose to end any treatment condition session or study assessment visit at any time if they believe (1) it is not in the best interest of the participant to continue (e.g. the participant becomes upset and/or is unable to continue, medical emergency, etc.) or (2) if staff believe their safety is at risk. Study staff will be trained in safety procedures to ensure their own safety when conducting study assessment visits. The same crisis reporting procedures for staff safety concerns will apply in terms of immediately contacting Drs. Ilgen or Lin, or a clinical supervisor or project manager on call. As part of the follow-up assessment protocol, written safety procedures for conducting community-based follow-ups include meeting at public locations, during daylight hours, in pairs, and with mandatory call-in procedures. Prior research conducted by the study team using such procedures with similar populations has resulted in minimal incidents where staff safety concerns became an issue during follow-up assessments. All safety concerns regarding follow-up assessments will be reported immediately to Drs. Ilgen and Lin. Individual study participation may also be ended by PI discretion. Reasons for involuntary study withdrawal will be included in the informed consent document and may include:

- It is not in the best interest or is harmful to the participant to stay in the study.
- The researcher believes the individual's participation is harmful to others or staff.
- A participant becomes ineligible to participate (e.g. no longer can provide voluntary consent, changes in competency, etc).
- A participant does not follow instructions from the researchers (e.g. does not complete any of the study sessions or is determined to be "lost to follow-up").
- The study is suspended or canceled.
- Other administrative reasons or unanticipated circumstances.

Once a participant has completed all study requirements, research staff will have no further contact with participants for this study. They may, however, be contacted again if they provide consent to be contacted for future research studies (e.g. contacted for qualitative interviews). Adverse events or unexpected outcomes (e.g. participant hospitalization or deaths) will not be monitored or reported once a participant has completed the final 12-month follow-up assessment study visit.

7. SAFETY ASSESSMENTS

Once a participant has been enrolled in the study, their safety will be monitored throughout their duration on study in a variety of ways. As lead PIs, Drs. Ilgen and Lin will have the ultimate responsibility for monitoring the overall safety of the participants in the study, determining whether an event is considered an adverse event (AE) or serious adverse event (SAE), and reporting events as needed to the appropriate committees and agencies. Local site study personnel will be expected to notify the lead PIs, Project Managers, or other designated coordinating center personnel of serious

adverse events, noncompliance, or other study related problems as soon as they are identified. In all instances where participant safety is a concern, the participant will be evaluated and connected with the appropriate level of treatment services necessary. Senior clinicians are always on call for consultation if a participant seems distressed or needs special attention. All participants are instructed on how to obtain emergency care, should that be required. As a requirement of the NCCIH, this study will also include an Independent Monitoring Committee (IMC) or other study monitor which may perform oversight functions and report their observations and findings to the IRB or designated official as needed. Functions could include: observing recruitment and enrollment procedures and the consent process for individuals, overseeing study interventions and interactions, reviewing monitoring plans, or overseeing data matching, data collection, and analysis. These monitors may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research. The IMC or any other monitoring entity will have authority to stop a research protocol in progress, remove individual subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects. Any patient safety events will be documented and reported to the appropriate entities (e.g. IRB, NCCIH, IMC, etc.) based on the study reporting requirements outlined below (see Section 7.4 "Reporting Requirements") and the Data and Safety Monitoring Plan (DSMP) for this study.

Given the characteristics of the study population (participants with OUD experiencing chronic pain on buprenorphine treatment), we anticipate there may be **expected** adverse events that participants may experience while on study in the following domains:

(1) **Acute Opioid Risk Situations**, where subjects may mention or endorse opioid use habits that acutely increase their risk of an overdose.

A brief risk assessment will be completed if the participant endorses or reports experiencing an overdose within the past 30 days and/or use of their buprenorphine in addition to the use of opioids or other medications in a way that would lead to acute overdose risk; including other substances that, if they were to take when they left, have a high likelihood of experiencing an overdose. This includes, but is not limited to: probable use of heroin, cocaine, benzodiazepines, prescription opioids or snorting or injecting their medication if it is not written as such. Specific procedures for identifying and responding to this type of risk are included below (see section 7.2 "Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters") and in the study Data and Safety Monitoring Plan (DSMP). The research staff member will follow the Opioid Risk Assessment Protocol developed for this study and consult with the PIs to determine whether the participant's distress was significant enough to warrant reporting such as an AE.

(2) **Breach of confidentiality** associated with data collection and necessary reporting of increased participant risk (suicide risk, homicide risk, or risk based on increased substance use) to appropriate authorities or health personnel.

There is a minor potential risk to confidentiality of assessment data and audio-recorded sessions. The risk of a violation of confidentiality exists because human participants will be disclosing personal information, both in assessments and therapy condition sessions. This risk is related to the damage that could be caused by an inadvertent release of sensitive information (e.g., psychiatric symptoms, substance use, etc.). Our research team has considerable experience in delivering study assessments in community locations while maintaining participant privacy as well as in maintaining the confidentiality of study data

and research records. Staff will have procedures in place to ensure data confidentiality (See Section 11.3 “Participant Confidentiality” for more details).

(3) **Homicidal ideation** as indicated by verbal report of thoughts of hurting others.

While the study does not directly ask about homicidal ideation, this information may be provided by the participant during an interaction with study team members. The protocol for handling homicidal ideation will be similar to that for suicidal ideation (see Section 7.2 “Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters”). Specifically, if the participant articulates thoughts of hurting others, the study team member will ask the participant to elaborate on his/her thoughts/behaviors (e.g., is there an identified victim, does the participant have a plan). The level of action necessary will be based on the participant’s responses and whether the study team member perceives that the patient or someone else is in immediate danger. Study personnel will follow established safety protocols and contact local licensed clinical staff when appropriate.

(4) **Hospitalization or Emergency Department/Urgent Care visits** as a result of mental health or substance use (e.g. acute intoxication, acute withdrawal, suicide attempts).

(5) **Severe Emotional Distress** as indicated by:

a. patient verbal report of a significant increase in psychiatric symptoms;

b. patients reporting significant distress due to the content of the self-report measures;

c. patients reporting significant distress due to the content of the PPMI or EUC conditions.

In each case, the research personnel will consult with the PIs to determine whether the participant’s distress was significant enough to warrant reporting as an AE.

(6) **Suicidal ideation** as indicated by:

a. self-report of significant suicidal ideations and behaviors on pertinent study questionnaires (e.g. a non-zero response on item #9 of the Patient Health Questionnaire (PHQ-9) or the response “on purpose, I wanted to die” or “I didn’t want to die but I didn’t care about the risks either” on item #7 within Overdose History after indicating an overdose in the past 30 days (item #3).

b. endorsement of recent suicidal thoughts, plans, or actions during the interview or assessment;

c. endorsement of thoughts of suicide or suicidal behaviors during the PPMI or EUC sessions.

In each case, the research personnel will follow the suicide risk assessment protocol (see section 7.2 “Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters” and the study Data and Safety Monitoring Plan) and consult with the PIs to determine whether the participant’s distress was significant enough to warrant reporting as an AE.

(7) **Psychological discomfort** as a result of being asked personal questions, particularly during the assessments and sessions. Participants may also become anxious or upset during discussions of their thoughts about issues such as their mental health treatment that occur during the sessions.

Study staff will be trained to respond to this discomfort, including receiving extensive crisis training and proper ways to refer participants to appropriate resources (i.e., treatment center staff, authorities, etc.) as necessary. Additionally, to minimize this risk, all participants will be informed of their right to refuse to answer any question they do not wish to answer and of their right to withdraw from the study at any time. Participants will also be informed that they can take breaks. There is a small risk that the PPMI and EUC conditions might upset participants. EUC sessions will focus on providing beneficial educational materials and participants will have opportunities to express and discuss any distressing thoughts or emotions these materials produce. The PPMI condition will utilize a CBT-based intervention. CBT for pain management approaches have established efficacy to improve pain-related functioning and it has been the experience of the project's investigators that these approaches dramatically diminish risks to participants from the study's intervention. Study therapist delivering both conditions will be masters-level therapists and will receive regular supervision by the Dr. Ilgen, who is a licensed psychologist, or other specified staff member/clinical supervisor. They will also receive intensive training in dealing with high risk patients.

Unexpected events are always possible in intervention research. Given the study population, it is possible that participants will report other serious psychiatric or medical symptoms not listed above. Research staff will be trained to monitor significant abnormal behavior and/or report that the participant perceives him/herself to be in imminent need of medical treatment. If it is determined that the participant requires immediate care, the research staff will contact local licensed clinical staff and coordinate appropriate services. We anticipate that there will be several triggers that will dictate when action may be required to protect patient safety. These may include the participant's expression of severe distress, suicidal or homicidal ideation, and/or other serious psychiatric or medical symptoms. Research staff will be required to review all self-report measures that may indicate an elevated risk for suicide or acute substance use risk before the participant leaves the assessment or concludes a study session. All research staff will be extensively trained and adequately prepared for situations in which a participant may express severe distress, dangerous substance use, and/or suicidal ideation. Subsequent to any participant's expression of severe distress, ideation, or other serious symptoms, project staff will make all reasonable attempts to re-contact the participant to monitor his or her well-being until the acute situation is resolved.

For those who report suicidal ideation, determination of high risk for suicidality will be based on a combination of the information gathered during the assessments or condition sessions (both self-report and verbal interview) and the interaction between the research personnel and the participant. All research staff will be trained extensively to respond to emotional distress and to discuss concerns and issues should they arise. All staff will be trained in the study specific risk management protocol, which will resemble a modified version of the VA/DOD Clinical Practice Guideline for Assessment and Management of Patients at Risk for Suicide. Our group has extensive experience with suicide risk management and have drafted detailed protocols for these situations (a copy of the risk assessment flowchart is included in the Appendix of this protocol for reference). More broadly, study staff will be trained to perform attentive and empathic listening as well as exhibit calmness during all participant interactions. If the participant articulates thoughts of death or suicidal ideation, the research team member will ask the participant to elaborate on recent suicidal thoughts/behavior, if the patient has not already provided adequate information to judge risk level. The level of risk will be based on the participant's responses and whether the research team member perceives that the patient is in immediate danger (e.g., an active plan with intent to act

verbalized). Any determination of risk level above moderate risk must be confirmed by the licensed clinical staff member on call. Study personnel will follow established safety and risk assessment protocols and contact local licensed clinical staff when appropriate. Participants who are determined to be at an elevated risk for suicide will be supported in a variety of ways depending on the participant's need, including but not limited to (1) referred to their treatment provider, (2) directly connecting suicidal participants to the 24-hour suicide crisis hotline, proper authority, or emergency psychiatric services, or (3) arranging with local psychiatry crisis management staff to assess and potentially hospitalize the patient as necessary according to the study protocol. Ongoing follow-up will occur until it is determined that risk is minimal. If disclosure is required for safety, participants will be encouraged to disclose suicidal ideation to their healthcare provider prior to breaking confidentiality. Participants will be notified prior to breaking confidentiality that research staff must disclose what was discussed between research staff and the participant in regards to current suicidal thoughts or behaviors to ensure the participant's safety. The incident report will also include documentation that the discussion between the participant and the research staff about breaking confidentiality occurred. Thorough documentation of the situation and all actions taken by research staff or other applicable treatment providers involved will be submitted for review by the research staff member to the project managers and PIs.

The following procedures will be used to address **online-survey** responses that indicate potential suicide risk:

(1) We will have an additional screen/page pop up for any participant who flags for suicide risk (e.g. endorses anything other than "not at all" on the PHQ item #9 asking about "thoughts that you would be better off dead, or of hurting yourself in some way" and/or endorses an overdose in the past 30 days on overdose history item #3 and indicates on item #7 the overdose was "on purpose, I wanted to die" or "I didn't want to die, but didn't care about the risks). The page will contain contact information for national and international suicide hotlines and web links to crisis centers. We will also include the study telephone number for non-emergencies. The URLs in the page open in a different window so the survey is not interrupted. These resources (and the health brochure) may be included in our study correspondence (i.e., letter, e-mail) regardless of risk level.

(2) The page will stay open for a minimum time period in attempts to assure the participant has read the information. The participant will not be able to close out of the survey until they check a box that indicates they have read and understand the information presented to them. This will confirm that the participant has viewed the information.

(3) REDCap will auto generate an email to the study team indicating "flagged" cases after the survey has been submitted. The email will have only the study ID.

(4) At least three attempts will be made to reach the participant by phone within 72 hours to further assess level of risk and/or answer questions. If the participant does not respond to research staff contacts attempts, the PIs will determine the appropriate course of action needed based on the risk level and situation.

Surveys completed via **postal mail** (we expect that this will be a very rare occurrence) may include the resource brochure which includes national suicide hotlines and mental health services. Surveys that are returned in which the participant endorses anything other than "not at all" for PHQ item #9 asking about "thoughts that you would be better off dead, or of hurting yourself in some way", endorses an overdose in the past 30 days, item #3 of the overdose history questions, and

indicates on item #7 “on purpose, I wanted to die” or “I didn’t want to die, but didn’t care about the risk,” or that indicate suicidal ideation or harm to others will be contacted by study staff. Study staff will make at least three attempts to reach the participant by phone within 72 hours of receiving the survey to further assess level of risk and/or answer questions. If the participant does not respond to research staff contacts attempts, the PIs will determine the appropriate course of action needed based on the risk level and situation.

In addition to suicide risk, all research staff will also be trained and prepared for situations in which a participant not currently in treatment reports severe substance misuse, for example if the participant has recently experienced increased substance use plus an emergency substance-related situation requiring immediate medical care (e.g. overdose) within the past 30 days. Our protocol in this regard is based on previous research that developed and implemented human subjects’ protections termed “rescue treatment” or “protective transfer” in studies of people with substance use disorders receiving less than standard treatment or having a poor response to standard or experimental treatments. In our study, participants who report at follow-up (during an interview or self-report measure) that they were hospitalized or made an emergency room or acute care outpatient visit due to acute substance use within the past 30 days will be protected by having project staff conduct a brief risk assessment and provide them with a resource brochure with local substance abuse resources and/or a referral to substance abuse treatment. Participants who require rescue treatment or immediate medical attention will be referred to the hospital or treatment provider closest to where they are residing. If the nearest facility is rejected by the participant for any reason, project staff will utilize SAMHSA’s online substance abuse treatment facility locator to provide a list of appropriate services.

During the conduct of clinical research with human participants for this study, there is the potential that an acute opioid risk situation will arise. For this study, this situation can include subjects who mention or endorse opioid use habits that acutely increase their risk of an overdose, or experiencing an overdose within the last 30 days. The following guidelines are designed to support project personnel in the management of these acute opioid risk situations. Specifically, these policies and procedures are designed to assist project personnel with identifying and contacting the health care agencies/resources that are the most appropriate for providing support in these specific instances. In all acute situations, project personnel should contact project managers and PIs as soon as possible, so that they can assist in the management of the situation.

Participants expressing acute overdose risk during an interview, or in response to a questionnaire will be assessed regarding risk level. We will use the same procedures described above for addressing on-line survey responses that indicate potential overdose risk. Based on the participants’ responses, research staff will focus on recent experiences (past 30 days) to assess current overdose risk level. Research staff will remind the participant of the exclusions to confidentiality that were covered in the informed consent process, and at the beginning of each assessment. Example consent language may include: “For this study, exclusions to confidentiality include child or elder abuse, harm to others or harm to yourself. Harm to yourself can include thoughts of suicide or using opioids in a harmful way. If any of these situations were to come up, we would talk to you more about it and may help you get in touch with others, including your provider or other authorities, to make sure that you are safe.” Participants will be encouraged to disclose aberrant opioid use or concurrent substance use with opioid prescription to their healthcare provider. Participants who are determined to be at a low or moderate risk for overdose will be provided with an overdose safety brochure with information on how to access naloxone. Research staff will encourage participants to talk to their current treatment providers or clinicians about their substance use. For

those participants who are no longer receiving treatment services, participants will be encouraged to re-engage in care and will be provided with a list of available treatment programs and resources that may be available to them. For participants who are determined, after the risk assessment, to be at high imminent risk for an overdose or are actively experiencing a substance-related crisis, research staff will contact 911 immediately. Research staff will remain with the participant until help arrives. All emergency actions as well as risk assessments conducted will be documented and reviewed by the PIs to ensure all safety protocols were followed.

7.1 Specification of Safety Parameters

Participants will be assessed for safety concerns throughout the study. The main safety concerns expected for this population revolve around risk of suicide and risk of increased substance use or overdose. All participants will receive a resource brochure at each study visit that will include information regarding substance use, warning signs of suicide, and resources and safety tips related to reducing overdose risk. This information is also available on the study website and a link to the information will be provided in all study correspondence. Specific questions will be asked of participants at each assessment that will evaluate risk and will trigger when an additional risk assessment will be conducted by research staff. These include the following:

- **Patient Health Questionnaire (PHQ-9)** *(administered at Baseline, 1-, 3-, 6-, 9-, and 12-month follow-up)*
    - Any participant who indicates a response greater than Zero ("Not at all") e.g. a "1", "2", or "3", on item #9 which states "Thoughts that you would be better off dead, or of hurting yourself in some way" will be assessed for suicide risk.

- **Overdose History Questionnaire** *(administered at Baseline, 1-, 3-, 6-, 9-, and 12-month follow-up)*
    - Any participant who indicates a response of "within the past 30 days" on item #3 which states "When was the most recent time you took too much drugs or medications/pills?" will be assessed for acute overdose risk.
    - In addition to #3 marked "within the past 30 days", a participant who indicates on item #7 a response of "on purpose, I wanted to die" or "I didn't want to die, but I didn't care about the risks" will be assessed for suicide risk.

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

All participants will be monitored for safety issues during their participation at all study visits, including condition sessions. Research study staff will be trained to identify and review all measures denoted as 'risk flags' prior to ending the assessment with a participant (or following completion of the online assessment). All participants who flag for an increase in risk to safety will be assessed by staff immediately after learning of the risk. Participants will be notified of the need for any consult with clinical supervisors should it arise. All incidents where increased risk was identified according to the parameters listed in section 7.1, or where risk was spontaneously generated by the participants during a study visit, will be documented using the study specific Risk Assessment Note. Routinely, the project managers will meet with PIs to analyze the Risk Reporting Forms to observe any patterns in participant risk status.

7.3 Adverse Events and Serious Adverse Events

For this study, we will utilize definitions for adverse events (AEs) and serious adverse events (SAEs) based on the University of Michigan IRBMED guidelines and definitions as follows:

- **Adverse Event (AE):** An adverse event (AE) is any experience or abnormal finding that has taken place during the course of a research project and was harmful to the subject participating in the research, or increased the risks of harm from the research, or had an unfavorable impact on the risk/benefit ratio. The event may or may not be caused by an intervention (e.g., headache following spinal tap, death from the underlying disease, car collision). Adverse Events also include psychological, social, emotional, and financial harms.
  - **Unanticipated Problems (UP):** Unanticipated problems involving risks to subjects or others include, in general. For an event or information to be considered an "unanticipated problem,"' three criteria must be met:
    - It must be "**unanticipated**." This means the event is **not** expected in terms of its nature, severity or frequency given the:
      - Procedures described in the study documents (e.g. the application, protocol, data and safety monitoring plan, etc.)
      - Characteristics of the subject population being studied (the traits, behaviors, symptoms, diseases, life experiences, or other qualities typically found in the persons comprising those eligible to participate in the study). A UP is a problem that was expected by neither the research participants nor the investigators (Note: This is not the same as the FDA definition of "unexpected")
    - It must be "**related to the research**." This means there is a reasonable possibility that the event or information may have been caused by, or is linked in a significant way, to the research. This encompasses all aspects of the research; it is not limited to test agents or procedures. It is also not necessarily limited to actions of the UM investigators.
    - The event or information suggests that the research places subjects or others at greater risk of harm than was previously known or recognized. This includes physical, psychological, economic, or social harm:
      - Type 1: Potential harm - Possibility that previously unsuspected harm may occur (or may occur at a higher than expected rate) even though no one has yet experienced actual harm.
      - Type 2: Actual harm - Recognized harmful or unfavorable outcome that has actually occurred to a research subject, a set of subjects, another individual being treated in a similar fashion in a relevant non-research setting, or another person connected to the research study.
- **Serious Adverse Event (SAE):** A serious adverse event (SAE) is one that meets one or more of the following criteria:
  - Results in death
  - Is life-threatening (places the subject at immediate risk of death from the event as it occurred)

- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.4 Reporting Procedures

This study will follow the University of Michigan IRBMED Multi-Site Research Reporting Plan. Please see details in this document in 15.2 Appendix B.

7.5 Follow-up for Adverse Events

Adverse Events will be followed for outcome information until resolution or stabilization. Attempts will be made to collect all relevant information regarding the event in order to properly report the event and determine the appropriate level of follow-up monitoring required. Adverse Events will not be monitored or reported once a participant is off study (e.g. completed their final research study visit [12-month follow-up assessment]).

7.6 Safety Monitoring

Safety monitoring will occur throughout the study as outlined by the Data and Safety Monitoring Plan. At least monthly but more frequently if necessary, the Project Managers will meet with the PIs to review all Risk Reports generated since the last review. These reports will include reports of (1) situations in which increased risk was identified during a study assessment per the guidelines outlined in Section 7.1 “Specifications of Safety Parameters”; (2) any AEs, SAEs, or UPs reported during the study; and (3) any protocol deviations or violations reported during the study. Any patterns of concern or deviations from the risk assessment protocols will be reported to the University of Michigan IRBMED, IMC, or other applicable reporting agency as necessary and outlined under Section 7.4 “Reporting Procedures”, the IMC Charter, or the Data and Safety Monitoring Plan.

An Annual Report will be compiled and will include a list and summary of AEs. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to the IRBMED and NCCIH. The IRB and other applicable recipients will review progress of this study on an annual basis. The study team will generate Study Reports for the Independent Monitoring Committee (IMC) using the NCCIH IMC Report Template. Information in the report will include protocol synopsis, enrollment and subject status, demographics and baseline characteristics, safety summary including adverse events, protocol deviations, quality management and outcomes data. Reports will not provide data on primary or secondary endpoints. Study Report tables will be generated only from aggregate (not by group assignment) baseline and aggregate safety data for the study population.

The IRB, IMC, and NCCIH Program Officials will receive copies of all study monitoring, audits, or inspection reports within 30 day of PI receipt.

8. CONDITION DISCONTINUATION

The Independent Monitoring Committee will review and decide on stopping rules for the study. This study will be stopped prior to its completion if: (1) the intervention condition is associated with adverse effects that call into question the safety of the intervention (e.g. there are significant differences [$p<0.01$] between PPMI and EUC groups in reported levels of AEs or SAEs); (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. Should the trial be stopped prior to its planned completion date for any reason, the PIs will report this stoppage to NCCIH in a reasonable time frame.

Participants may decide to discontinue their participation for any reason, at any time. Any participant requesting to withdraw their participation from the study, either by verbally communicating this information to a research staff member or through written communication (e.g. e-mail, mail, or text message) will no longer be contacted by study staff and their participation in the study will be considered complete. Participant data collected prior to the participant's decision to withdraw from the study will be used in data analyses unless the participant has specifically requested their data be removed. Participants may choose to discontinue participation in the intervention portion of the study (e.g. PPMI or EUC sessions) and will remain active in the study and continued to be followed with their permission. Research staff may choose to end any assessment or condition session early, using clinical discretion, if (1) they believe it is in the best interest of the participant (e.g. the participant becomes upset and/or is unable to continue, medical emergency, etc.), or (2) if staff believe their safety is at risk. As noted above, individual study participation may also be ended by PIs discretion. Reasons for involuntary study withdrawal will be included in the informed consent document and may include: (1) if it is not in the best interest or is harmful to the participant to stay in the study; (2) if the researcher believes the individual's participation is harmful to others or staff; (3) the participant becomes ineligible to participate (e.g. no longer can provide voluntary consent, changes in competency, etc); (4) the participant does not follow instructions from the researchers (e.g. does not complete any of the study sessions or is determined to be "lost to follow-up"); (5) the study is suspended or canceled; or (6) other administrative reasons or unanticipated circumstances.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

To minimize the likelihood of Type I errors, analyses for testing the main study hypotheses will be planned a priori and will be limited to the examination of a set number of outcomes. In addition, analyses that are central to the purpose of the study will be clearly identified as confirmatory hypotheses and will be clearly identified as separate from exploratory analyses. Prior to hypothesis testing, data will be examined and described using standard univariate summary measures and bivariate statistical measures of association, as well as graphical displays of the distribution of responses on all variables. Statistical assumptions required for the methods of analysis outlined in this section will be rigorously tested. Distributions of measures such as intensity and frequency of

pain, counts of buprenorphine non-adherence over follow-up, pain related functioning scores, and frequency of substance use that have multiple items and/or have potentially non-linear distributions will specifically be examined graphically to understand their distribution. The failure of statistical assumptions necessary for the techniques planned will be addressed using: 1) a different method of analysis (e.g., using a different link function in generalized linear models that is appropriate to the data distribution, using non-parametric tests instead of parametric tests); or 2) the data will be appropriately transformed to a distribution that meets the assumptions of the proposed statistical test.

Many of the proposed analyses involve the examination of differences over follow-up between the participants of the PPMI and EUC groups. Every effort will be made to ensure balance between groups on key characteristics during randomizations, with checks on the randomization on an ongoing basis during the study.

To minimize missing data, we will make every effort to gather follow-up information for all participants. Specific strategies to retain participants that have proven successful in our prior research are described above. We have also chosen analytic methods that will maximize the number of participants who will be included in analysis. Nonetheless, if our examination of the pattern of 'missingness' suggests that our assumptions are unsuitable for the models, we will handle missing data via multiple imputation procedures as described by Schafer.

The primary goal for the RCT is to examine the efficacy of PPMI by testing differences between the PPMI and EUC conditions on primary and secondary outcomes over 3-months and 12-months of follow-up. The primary analyses will involve calculating the attrition rates up to the first 3-months of follow-up. The secondary analyses will involve up to the 12-month follow-up. We will also examine the impact of telehealth PPMI on pain level, pain-related functioning, and frequency of substance use, including prescription and non-prescription opioid use at these two time points. We will also quantify session attendance and note the percent of participants who did not complete all sessions to identify ways to decrease drop-out and non-compliance to the intervention.

9.2 Sample Size and Randomization

Sample size estimates were guided by our prior work on psychosocial interventions for pain during addiction treatment and prior trials that used MAT retention as an outcome and calculated using Stata. In studies of buprenorphine programs, retention varies widely but generally is around 50% in studies with at least 3-months of follow-up and robust sampling.[26] For a time-to-event analysis we assumed an event rate of 50% in EUC, where the event is dropping out of treatment, and based calculations on a two-sided α=0.05. A hazard ratio of 0.5 (i.e., PPMI less likely to drop out of treatment) would achieve >85% power with a sample size of 200, or 100 per group. Given that we will be able to infer treatment retention even for participants who drop out of the study, our primary outcome analysis was based around our complete sample size of 200.

9.2.1 Treatment Assignment Procedures

Details regarding how participants will randomly be assigned to one of the two study conditions (PPMI vs. EUC) are described above (see Section 5. "Study Conditions", Section 6.2.2 "Enrollment, Baseline, and Randomization", and Section 6.2.3 "Blinding").

Randomization will be stratified by gender (biologically assigned male versus biologically assigned female at birth), past year use of heroin (yes/no), and veteran status (community/veteran). There is no sample size goal for each stratum, although strata assignment

and condition assignment will be monitored throughout the study to ensure an imbalance does not occur that could impact the ability to report on main study outcomes. Data on adherence to the intervention condition's protocol will be collected monthly by research staff and reviewed monthly by the PI/Project Managers. Adherence of participants will be evaluated by the Project Managers. If adherence falls below the expected rate, which might inhibit the ability of the study to test its primary hypotheses, the Project Managers will suggest a conference call for study investigators to discuss methods for improving adherence.

9.3 Definition of Populations

For this study, analysis will use an intent-to-treat (ITT) framework, where participants are classified by the condition they were randomized to, regardless of what they received. Cox Proportional Hazards regression models will be used to test the association between group assignment and time to dropping out of buprenorphine treatment. We will test whether the assumptions for this modeling technique are met, and if they are not, consider variable transformations or alternative modeling strategies (e.g., generalized linear models).

While primary analyses will use the ITT framework, we will further examine treatment effects by conducting a per-protocol analysis. As stated earlier (see Section 5.4 "Adherence Assessment"), participants will be considered to be "per-protocol" if they complete at least 4 sessions of the PPMI condition, or 1 session of the EUC condition. This cutoff equates to receiving 50% of the proposed material which will be sufficient to consider the intervention condition being received by the participant. Prior to conducting this analysis, we will verify the assumption that this cut-off represents a level of treatment compliance for participants (as intended by the study design) by comparing the associations of patient characteristics with the likelihood of attending six or more sessions. If this assumption is not met, we will consider alternative methods for comparing condition groups, such as complier average causal effect models, which use latent variable/training data methods to assign compliance levels for EUC group participants.

9.4 Interim Analyses and Stopping Rules

There are no formal interim analyses planned for this RCT. Recommendations of the Independent Monitoring Committee, IRB, the sponsor(s), or relevant local regulatory authorities, which may include review of serious, unexpected, and related AEs may result in suspension of further study conditions at a site. The study sponsor(s) retain the authority to suspend additional enrollment and study conditions for the entire study, as applicable. Findings that might trigger a safety review are the number of overall SAEs, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events.

9.5 Outcomes

All outcome measures for this study have been selected to include high reliability, validity, and variability. Most measures have been utilized in prior research examining similar populations of interest (e.g. those with pain, those with substance use disorders, etc.). All outcomes from this study will be patient-reported outcomes (PROs), which have been widely used in clinical research trials.

9.5.1 Primary Outcome

The **primary outcome** of interest is retention on buprenorphine treatment or remaining engaged in buprenorphine treatment over a 3-month period. We hypothesize that

participants receiving the PPMI condition (intervention condition) will have higher levels of retention on buprenorphine treatment over the 3-month follow-up period when compared to participants who receive the EUC condition (control condition). For **Primary Aim 1**, retention on buprenorphine treatment will be measured using data collected from the weekly surveys and the Time Line Follow Back (TLFB). Participants will have the opportunity to complete a total of 13 surveys over the course of the first 13 weeks of the study. During these weekly surveys, participants will be asked to respond to three questions that will be used to measure treatment retention: (1) a dichotomous questions regarding treatment engagement status ("Are you still being prescribed buprenorphine as a treatment for problematic opioid use?"); (2) a question regarding number of days that the participant has taken their medication recently ("On the calendar below, please check off each day that you have taken your buprenorphine out of the past 7 days."); and (3) a dichotomous question regarding overall buprenorphine treatment engagement since the beginning of the study ("Since you began this study on ____{DATE}_____, has there been any time when you went for at least 7 days at a time WITHOUT taking your buprenorphine for any reason?"). Data from these weekly surveys is expected to have greater specificity than data collected during the follow-ups due to the nature of the data collection (i.e. each week versus retrospectively over several months). This weekly survey data will be utilized to guide the discussion of the TLFB during the 1- and 3-month follow-up in order to ensure all data is captured. The main outcome measure used for data analyses, therefore, will be the TLFB.

For **Secondary Aim 1**, retention on buprenorphine treatment will be measured using data collected during the Time Line Follow Back over 12-months. The Timeline Follow-Back Assessment of Substance Use (TLFB) protocol examines daily alcohol and other drug consumption over specified time intervals (e.g., 90-180 days) using monthly calendars. Several studies have demonstrated the reliability and validity of this method of assessing alcohol use using test-retest and convergent methodologies, and a recent study supports the reliability and validity for assessing drug use. Utilizing the TLFB, we will be able to collect alcohol use, drug use, and buprenorphine treatment data (including number of days the participant has taken their medication) throughout the entire follow-up period (12-months post study enrollment).

The secondary outcomes are hypothesized to meet the assumptions of continuous variables, and we will consequently use t-tests to make comparisons. If, however, the distribution of a measure is skewed, alternative modeling strategies will be used. In all analyses, we will use an intent-to-treat framework. Pain level will be measured using the Numeric Rating Scale for Pain Intensity (NRS-I), an 11-point numeric rating scale (0 = no pain, 10 = worst pain imaginable). All participants will be asked to rate their usual and worst pain over a specified time frame (e.g. past week, past 3 months, since last visit, etc.) We will take the average of these ratings as the primary measure of pain intensity. Participants will complete the NRS-I during all assessments, including the weekly surveys. Frequency of substance use will be measured using the Time Line Follow Back Interview (TLFB), a calendar-assisted structured interview that provides the participant with temporal cues to increase the accuracy of recall. Participants are asked to recall how much they drank or used any other controlled substances on each day during the specified time frame, starting with the most recent day and progressing back one day at a time. The interviewer-administered instrument has demonstrated test-retest reliability of greater than 0.86. Percent days abstinent from alcohol and drugs will be used as the primary measure of substance use at

each assessment time point (baseline enrollment assessment and 3- and 12-month follow-up assessments).

The primary outcome measure for this study is retention on buprenorphine treatment as measured over 3-months. Secondary Aim 1 for this study is retention on buprenorphine treatment over 12-months. This will be operationalized as time to first episode of buprenorphine treatment non-adherence. Non-adherence, or discontinuation of treatment, will be defined as a consecutive period of 7 or more calendar days without taking buprenorphine. Buprenorphine retention will be collected in a variety of ways for this study:

(1) as part of the TLFB assessment, which will be administered at the baseline enrollment assessment and the 1-, 3-, 6-, 9-, 12-month follow-ups in which the participant will be asked to recall on which days they took their buprenorphine medications;

(2) as part of weekly surveys completed during the study;

(3) through medical record reviews at the treatment sites (as applicable when participants and clinics have provided proper releases of information) to review urine toxicology screens and/or prescription fill records;

(4) through urine analysis at 1-, 3-, 6-, 9-, and 12-month follow-up

Medical Records will be reviewed, when applicable, for the following piece of information regarding buprenorphine treatment: (1) number treatment appointments scheduled with the buprenorphine provider, (2) number of treatment appointments completed with the buprenorphine provider, (3) number of treatment appointments scheduled but not completed by the participants with the buprenorphine provider, (4) urine toxicology results obtained as part of buprenorphine treatment only, (5) prescription fills for buprenorphine prescriptions through the VA pharmacy. The research team has extensive experience obtaining prescription fills and other data through CPRS from prior studies.

9.5.2 Secondary Outcomes

The **secondary outcomes** of interest are pain level, pain-related functioning, and frequency of substance use. We hypothesize that participants receiving the PPMI condition (intervention condition) will report less pain, an increase in pain-related functioning, and lower frequency of substance use over the 3-month (Secondary Aim 2) and 12-month (Secondary Aim 3) follow-up period when compared to the EUC condition (control condition).

These outcomes for both **Secondary Aims 2 and 3** will be measured in the following ways:

- **Pain level** will be measured using the Numerical Rating Scale for Pain Intensity (NRS-I), which will be collected at all time-points. For each follow-up time point, we will subtract the baseline value to obtain a change score. For this study, a clinically significant change in pain level will be operationalized as a 30% reduction of pain, which would equate to change of 2 points on a 0 to 11 pain intensity numerical scale such as the NRS-I.
- **Pain-related functioning** will be measured using the pain interference subscale of the Brief Pain Inventory – Short Form (BPI) . The BPI Short Form is a widely used, validated measure that assesses both pain level and the impact pain has on functioning over the past 24 hours. For each follow-up time point, we will subtract the baseline value to

obtain a change score. For this study, an increase in pain-related functioning will be operationalized as a reduction in the pain interference scale scores over time.

- **Frequency of substance use** will be measured using the TLFB, which will be collected at all follow-up time-points. During this administration, the participant will be asked to recall their alcohol and drug use since the previous follow-up time point. Percent days abstinent from alcohol and drugs will be used as the primary measure of substance use at each assessment time point (baseline,1-, 3-, 6-, 9-, and 12-month follow-up assessment).

To accomplish **Secondary Aim 4** (qualitative interviews for rapid implementation), a random sample (n=20) of participants who completed the PPMI condition will be interviewed in addition to a sample (n=15) of buprenorphine providers/clinic staff.

9.6 Data Analyses

This study will utilize an intent-to-treat approach where the primary analyses will examine the association between randomization to condition and the treatment outcomes, irrespective of how much of the intervention or control conditions the participants attended. However, in exploratory analyses, the study will explore how controlling for session attendance influences the primary results and whether session attendance mediates the potential effects of assignment to treatment condition on the subsequent outcomes. The PI, data manager, and project biostatisticians and/or data analysts will analyze the data using SAS software. The primary specific aims will focus on pain (level, tolerance and pain-related disability) and substance use (frequency of drug, alcohol and opioid use) outcomes. Outcome data will be analyzed using mixed model regression analyses. The alpha level will be set at 5%.

As stated previously, the primary aims are:

Primary Aim 1: Conduct a randomized controlled trial (RCT) comparing a remotely delivered PPMI (n=100) to EUC (n=100) to assess the impact of randomization to PPMI on retention on buprenorphine treatment over 3-months.

Research Hypotheses for Primary Aim 1: Participants in the PPMI condition will have greater retention on buprenorphine treatment (i.e., lower treatment dropout): up to 3-months. The primary goals for the project are to test the preliminary efficacy of an 8-session Psychosocial Pain Management Intervention (PPMI), as compared to an EUC control condition, on retention on buprenorphine treatment. We will evaluate measures of self-reported information gained from the TLFB on buprenorphine treatment use on a daily basis and data collected from weekly surveys completed by the participant. For those with multiple sources of information available (TLFB and self-report survey), we will use the comparison between sources of data to develop reasonable assumptions about actual consumption. It is anticipated that individuals will occasionally miss a day of buprenorphine treatment without having dropped out of treatment. Discontinuation of treatment will be operationalized as 7 days in a row without taking buprenorphine. Analysis will follow a time-to-event (survival analysis) framework where the outcome is time until discontinuing buprenorphine treatment.

We will first descriptively calculate the percent still receiving buprenorphine at the 1- and 3-month follow-ups. The independent variable of interest is an indicator of group (PPMI vs.

EUC). Analysis will use an intent-to-treat framework, where participants are classified by the condition they were randomized to, regardless of what they received. Cox Proportional Hazards regression models will be used to test the association between group assignment and time to dropping out of buprenorphine treatment at 3-months. We will test if assumptions for this modeling technique are met, and if they are not, consider including a covariate*time interaction or stratification in Cox modeling, or variable transformations or alternative modeling strategies, if necessary.

The secondary aims are:

Secondary Aim 1: Conduct a randomized controlled trial (RCT) comparing remotely delivered PPMI (n=100) to EUC (n=100) to assess the impact of randomization to PPMI on retention on buprenorphine treatment over 12-months.

Secondary Aim 2: Determine the impact of remotely delivered PPMI on pain level, pain-related functioning, and frequency of substance use over 3-months.

Secondary Aim 3: Determine the impact of remotely delivered PPMI on pain level, pain-related functioning, and frequency of substance use over 12-months.

Research Hypotheses for Secondary Aim 1: Participants in the PPMI condition will have greater retention on buprenorphine treatment (i.e., lower treatment dropout) over the entire 12-months of follow-up. The primary goals for the project are to test the preliminary efficacy of an 8-session Psychosocial Pain Management Intervention (PPMI), as compared to an EUC control condition, on retention on buprenorphine treatment. We will evaluate measures of self-reported information gained from the TLFB on buprenorphine treatment use on a daily basis and data collected from weekly surveys completed by the participant. For those with multiple sources of information available (TLFB and self-report survey), we will use the comparison between sources of data to develop reasonable assumptions about actual consumption. It is anticipated that individuals will occasionally miss a day of buprenorphine treatment without having dropped out of treatment. Discontinuation of treatment will be operationalized as 7 days in a row without taking buprenorphine. Analysis will follow a time-to-event (survival analysis) framework where the outcome is time until discontinuing buprenorphine treatment.

We will first descriptively calculate the percent still receiving buprenorphine at the 6-, 9-, and 12-month follow-ups. The independent variable of interest is an indicator of group (PPMI vs. EUC). Analysis will use an intent-to-treat framework, where participants are classified by the condition they were randomized to, regardless of what they received. Cox Proportional Hazards regression models will be used to test the association between group assignment and time to dropping out of buprenorphine treatment at 12-months. We will test if assumptions for this modeling technique are met, and if they are not, consider including a covariate*time interaction or stratification in Cox modeling, or variable transformations or alternative modeling strategies, if necessary.

Research Hypotheses for Secondary Aims 2 and 3: Compared with participants randomized to the EUC (control) condition, participants randomized to the PPMI condition will report a greater reduction in pain level, an increase in pain-related functioning, and a decrease in frequency of substance use at: (1) 3-months; and (2) 12-months post-intervention. We will calculate the

means and standard deviations for these outcomes at baseline, 1-, 3-, 6-, 9-, and 12-months, as well as change scores from baseline for the two groups. We hypothesize that participants randomized to the PPMI will have less pain, better functioning, and lower frequency of opioid use at follow-ups compared to EUC. These secondary outcomes are hypothesized to meet the assumptions of continuous variables, and we will consequently use t-tests to make comparisons. If, however, the distribution of a given outcome measure is skewed, alternative modeling strategies will be used. We will use a linear mixed-effects model and estimate the treatment effect as the difference in the time-averaged changes from baseline in pain levels (using the NRS-I) and in pain-related functioning (using the BPI) over the course of follow-up (namely, at 3-months for secondary aim 2 and at 12-months for secondary aim 3). Because reduction in pain is of key interest, the analysis will model change-scores from baseline in the response variable as the dependent variable, and the independent variables will include the baseline values of the response variable, time in months since randomization and the treatment group indicator. The parameter estimate of the treatment group indicator will estimate the time-averaged treatment effect. If the graphical exploration (described above) shows potentially differential linear decrease in pain over time, we will include an interaction of time by treatment group indicator to model and test for this. For frequency of substance use, we will first assess the distribution of measures collected to assess alcohol use, illicit drug use and prescription opioid medication use to determine whether a summary or composite measure of each of these may represent the use or misuse more appropriately. For example, illicit drug use will be obtained as the number of days the participant used each of multiple drugs, and thus we may consider combining the days of any of the illicit drug use. We will also combine the alcohol and drug use data obtained using TLFB interviews as the percent days abstinent from alcohol and drugs during the past 30 days at each assessment time. We will then check the distribution of the substance use and prescription medication misuse (measured using the TLFB), and unless the data are highly skewed, we will use a linear mixed-effect model to test the hypothesis and to estimate the treatment effect as the difference in the time-averaged changes from baseline in these outcome measures over the course of the 12-month follow-up period.

Secondary Aim 4: Facilitate the rapid implementation of results by gathering qualitative data from key stakeholders including MAT treatment providers (n=15) and patients who received the telehealth PPMI condition (n=20).

Research Hypothesis for Secondary Aim 4: We will follow a comprehensive plan to integrate quantitative and qualitative data to more rapidly enable future implementation of the intervention in patients receiving buprenorphine for OUD. First, this study is a mixed-methods hybrid type I study specifically guided by the widely-used RE-AIM framework, which provides essential elements to consider to understand barriers and facilitators to future implementation. We will address key specific questions that we will be able to answer through our qualitative and quantitative data and how they will inform our understanding of future implementation as guided by the specific elements of RE-AIM. Second, we are using a rapid analysis approach in our qualitative interviews, a specific deductive approach using semi-structured interviews to produce actionable information from qualitative data in a timely manner. We will organize the summarized qualitative data using matrices, which will increase efficiency of analyzing the data and synthesizing overall findings. Finally, our team has extensive methodological expertise in conducting mixed-methods substance use disorder intervention studies to enhance future implementation.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Data will be collected following consent from the participant (either electronic or verbal for eligibility screening, and written or verbal consent for the RCT). All forms used for data collection throughout the study will be approved by NCCIH, the IRB, and all PIs prior to implementation as data collection or tracking forms. All staff will receive training on the proper use and storage of all data collection forms and source documents. Data may be collected for this study using a variety of modalities, based on availability at the site and patient preference, and include:

- data collected in-person by research staff using standardized paper forms
- data collected in-person by research staff using REDCap survey via tablet (electronic data capture [EDC])
- data collected remotely from the participant via REDCap online survey (electronic data capture [EDC])
- data collected by research staff via telephone, video chat, and/or US postal mail with responses captured by the researcher either via tablet or computer (through a REDCap assisted survey), or via paper/pencil collection

All data collected will only be identified with the participant's unique study identification numbers and will be kept separate from any identifiable information (either in a separate physical location for paper data or in a separate electronic database for electronic data). This participant study identification numbers will appear on all study data forms and materials, rather than the participant's name or other identifiable information. All data will be stored securely at all times during the study and will be stored based on the data safety requirements of the local site. For any sites that do not have specific data storage requirements, the standard data security requirements of the University of Michigan IRBMED will be used, which includes ensuring that any study forms or documents that contain participant's names and other identifying information will be kept separately from study data on password-protected files on a secure server with restricted access and/or in a locked cabinet in a locked room; and only participants' unique ID number will be kept in the database on password protected file. VA participant audio recordings will be stored on a VA protected server behind a VA firewall. VA consent forms and locator forms will be stored within a locked cabinet within a VA secure office space.

Because this is a longitudinal study in which participants will be contacted a number of times and data will be linked, via a crosswalk file containing contact information linking participants' identifiers with their unique study identification number will be stored separately from any participant data on a secure server in a password protected file. No identifiers or crosswalk for VA participants will be stored at UM. Only coded data will be collected, stored and analyzed at UM. All identifying information of VA participants will be stored on the VA network. Access to electronic data files and folders will be restricted to research staff as noted in the local site IRBs.

Throughout the study, participants will be asked to respond to questions using self-report surveys and research administered interviews on topics such as pain level and related conditions, general health and mental well-being and functioning, substance use, and

buprenorphine treatment involvement and satisfaction. All data collection forms will be reviewed by the Coordinating Center PIs (Drs. Ilgen and Lin), project managers, and data manager/data analyst before implementation. Since some study visits will take place at either local study sites or in the community, data will be collected offsite and will be transported to specified data storage locations with the use of a locked box or brief case and will be kept with study staff at all times.

With participant permission, PPMI and EUC sessions and the qualitative interview (conducted as part of Secondary Aim 4) will be audio-recorded to ensure therapist and research staff fidelity to the session content and for transcription of the qualitative interviews for analysis. PPMI and EUC sessions will be audio-recorded for treatment fidelity, and will take place over the phone or video chat. Participants may choose the video chat platform most convenient for them (e.g., Zoom, BlueJeans, FaceTime or Skype for Business) for sessions and interviews, however, HIPAA compliant platforms (e.g., Zoom) will be recommended and encouraged. Qualitative interviews will take place in-person whenever possible but may also be conducted over the phone or via video chat at the request of the participant. The audio recordings for the PPMI and EUC sessions and qualitative interviews will be done with a digital voice recorder approved for use at local sites as necessary. The audio-recordings of the interviews will be destroyed after the files are uploaded to a password-protected, secure server with restricted access. Participants will be asked not to mention names or other identifying information in during the recorded interview. Any identifying information will be removed from transcriptions.

Paper copies of interview questions and notes may be kept along with the transcript of the qualitative interviews in the participants' research file. All project staff members are responsible for reviewing the data provided by the participant following collection to ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Once collected, participant data will remain confidential. Only study team members who have completed appropriate training in the protection of human subjects at the VHA and University of Michigan or other local site requirements will have access to the data. Hard copies of data will be stored in a locked data storage room in a University of Michigan secure cabinet. Electronic data will be stored on a secure UM server on password-protected files and coded by subject identification number so that participants cannot be identified by their research record. Any data collected via pen and paper, such as tracking forms, will be manually entered into the study REDCap database using double entry when possible. Data cleaning will be conducted throughout the data collection period to ensure the production of a final dataset for analysis at the end of data collection. Regulatory Binder information may be in the form of both electronic and hard copy files. These binders will be stored in the same manner as study data described above. Physical security of data will be assured by daily and weekly back-ups.

Data quality will be monitored by random inspection of the completed forms by the project managers and/or research associate and any problems detected will be discussed with the PIs. The project managers will also periodically observe research staff completing study activities (such as the informed consent process, study assessments, entry of study data into project databases, documenting study activities, etc.) to assure all procedures are being followed according to the protocol. The project managers may additionally contact

participants following completion of study assessments to ensure that project staff members completed all study tasks and followed procedures during the assessments. Any deviation to the protocol that may have an effect on the safety or rights of the participant or the integrity of the study will be report promptly to the appropriate agencies and boards per our reporting plan, and will result in staff re-training. Quality and delivery of both the PPMI and EUC sessions will be monitored by the PIs, project managers, and/or research staff responsible for providing therapist and research staff supervision. Adherence to therapy techniques will be monitored using audiotapes and individual supervision according to the protocol for the PPMI condition. If PPMI therapy drift is observed, the therapists will be re-trained appropriately. The project managers will also periodically look at eligibility criteria, participant recruitment and retention numbers, and randomization tables to determine they are accurate and up to date. Project managers and other research staff will communicate regularly to monitor study progress.

10.2 Data Management

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation. Data collection and accurate documentation are the responsibility of the study staff under the supervision of the principal investigator and project managers. The Coordinating Center will be responsible for ensuring that all supporting sites are utilizing the correct versions of all forms and data collection instruments and that all data is collected in a standardized manner. All source documents will be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events will be reviewed by the PIs (Drs. Ilgen and Lin) or project managers.

Drs. Ilgen and Lin, local site PIs and any Co-Investigators, the Project Managers, Data Manager and Analysts will meet at least monthly (or more frequently as needed) to discuss the development of the data management system (from collection by Research Assistants to analysis), training of data entry, data safety, coding and cleaning of data. We have found that it is beneficial to include Research Assistants in these meetings, when possible, so the data decisions can be implemented in real-time during collection, entry, and cleaning. The data manager will be responsible for the oversight of data quality and will report any irregularities or measure administration errors to the Project Managers. Both the Project Managers and Data Manager will address these issues with the appropriate staff member to correct any discrepancies and errors in the data collection and entry process. To minimize the violation of confidentiality, we will ensure that data are protected and cannot be linked to a particular person. Unique identification numbers will be assigned to each participant and all data are coded with this number, rather than by name. All hard copy data are stored in University of Michigan access restricted space in locked file cabinets. Consent forms will be stored separately with limited access on a secure server, because they contain identifying information. Data entry staff will work with forms that contain only subject numbers.

Physical security of data will be assured by daily and weekly back-ups. Electronic communication with outside collaborators will involve only unidentifiable information.

The on-line surveys will be designed and administered using the University of Michigan REDCap (Research Electronic Data Capture), which will be used for data collection and storage during the study. Participants' names and contact information will be stored in a secure REDCap database, separate from their study data and only accessible to members of the research team for research purposes. Only research staff members listed on IRB approved applications will be granted access to the REDCap databases. VA participants will provide HIPAA authorization, included in the informed consent document, for their coded assessment data to be collected directly into UM REDCap. We will also obtain a Data Use Agreement between UM and AAVA for this process. Assessments will be completed via phone with study staff who will enter data directly into REDCap or self-administered by participants. Data may also be entered into REDCap by research staff from surveys completed via paper and pencil. VA participants will be asked via informed consent for permission to receive emails from the study VA email account. For self-administered assessment completion, VA email messages will be sent to participants (emails will not be sent through REDCap but rather encrypted through the study VA email account) that will contain a link and instructions for completing the REDCap surveys on their own devices. UM REDCap will contain only coded assessment data for VA participants. REDCap is a secure web application designed to support data capture for research studies. It provides user-friendly web-based case report forms, real-time data entry with branching logic and validation (e.g. for data types and range checks), audit trails, a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus), procedures for importing data from external sources, and advanced features such as a data quality check module. The system was developed by a multi-institutional consortium initiated at Vanderbilt University. REDCap servers are physically located in the University of Michigan Medical School Information Systems (MSIS) data center. Application and database servers are on virtual machines (VM). The VM servers are Red Hat Enterprise Linux Server 5.6 (64-bit, 2.6.18 238 e15-smp kernel) 2x AMD Opteron 6174 5.0.95 2.2 GHz with 4 GB RAM, running Apache 2.2.3 (application servers) and MySQL (database servers). Physical security for the databases is provided in a professionally managed and equipped tier-2 data center with tightly controlled access. Remote data access employs SSL encryption and 2-tier Kerberos/Level 1 and UMHS Level 2 password challenges via LDAP authentication. Access to the application, the database, and the underlying systems infrastructure are consistent with industry best practices including HIPAA security and privacy requirements and the HITECH Act. The application provides audit trails on user access to MICHR and MSIS technical and support teams. Backup of data is managed by MSIS and vulnerability testing is performed regularly by the University of Michigan Health System Medical Center Information Technology (UMHS MCIT). Risk evaluation is performed using a methodology derived from NIST Special Publication 800-53 – "Recommended Security Controls for Federal Information Systems" and is used to refine and improve operating policies and procedures. Daily backups and VM snapshots of the application and database servers are stored on a remote storage device. The restoration of the servers from a hardware or software failure are protected for 24 hours of disaster recovery.

VA Informatics and Computing Infrastructure (VINCI)

We may request data extracts from the VHA Corporate Data Warehouse (CDW) for VA patient participants. VINCI is a partner with the Corporate Data Warehouse and hosts all data available through CDW. As VA and VHA research progresses, large amounts of data are being collected into databases maintained by a variety of investigators, studies, and locations. Individual investigators and multiple databases may lack sufficient resources to ensure consistency and quality control, or a long-term commitment to data storage and access. Therefore, there are less consistent standards for the protection of Veterans data, data quality, and data access compared to a centralized repository. A centralized research data repository, such as the VA Informatics and Computing Infrastructure (VINCI), offers a number of important advantages: Consistent, defined, and transparent security and standards for access to data; a common point of entry for all investigators who use the data; tools for analysis and reporting; tighter and more consistent control over the standards and quality of the data included; and the ability to standardize and update terminology and format as technology and methodology improve. VINCI is a partnership between the VA Office of Information Technology (OI&T) and the Veterans' Health Administration Office of Research and Development (VHA ORD). VINCI provides the storage and server technologies to securely host suites of databases integrated from select national data. These servers reside at the Austin Information Technology Center (AITC), located in Austin, Texas. To ensure the protection of Veterans data, VINCI maintains compliance with the guidelines set forth by Veterans Health Administration (VHA) Handbook 1200.12, Use of Data and Data Repositories in VHA Research and all other applicable VA and VHA policies and regulations. In addition, VINCI has undergone all security certification activities in support of obtaining an Authorization to Operate (ATO). Access to VINCI resources will be approved in accordance with the requirements of National Data Systems (NDS), VHA Handbook 1200.12, Use of Data and Data Repositories in VHA Research, and all other applicable VA and VHA policies and regulations. Researchers and Operations staff will access the data along with the tools for analysis and reporting in the secure, virtual working environment through a certified VHA network computer using the VA INTRANET (NOTE: VINCI is not accessible through the INTERNET). If not working within a VA or VHA hosted office environment containing VA network access, researchers may access VINCI through an approved Virtual Private Network (VPN) and Remote Desktop application. The remote computing environment will enable data analysis to be done directly on VINCI-CDW servers located at the Austin Information Technology Center, thus keeping all data from being transmitted to local PC hard drives.

VINCI Data Collection

VA provides care to veterans at over 1,400 points of care. At the core of virtually all care processes is a broadly scoped and extensively used electronic health record system known as the Veterans Information System Technology Architecture (VistA). VistA provides a longitudinal view for patients receiving care nationwide including diagnosis, procedures, pharmacy, orders, labs, microbiology, physiologic measurements, and text documents. VA uses 128 VistA implementations to provide longitudinal electronic health record services nationwide for more than 25 million veterans historically. The aggregate content of these 128 VistA systems includes just over 1.03 Billion documents (e.g., Progress Notes, Discharge Summaries, Reports) accumulating at a rate of 638,000 each workday; 1.65 Billion orders (+955,000 each workday); 590 Million images (+884,000 each workday); 1.06 Billion vital

sign measurements (+729,000 each workday) and 850 Million medication administrations (+607,000 each workday).

VA Informatics and Computing Infrastructure (VINCI) aggregates data sources from individual VistA systems, data from the Regional Data Warehouses for all 4 VA regions, the VA Corporate Data Warehouse, and the VA Health Data Repository and prepares them for research use. Other data published by the VHA Decision Support System (DSS) and Inpatient and Outpatient Medical SAS (MedSAS) can be requested through VINCI. VA National Data Services and other data stewards regulate the right to use the data, but VINCI facilitates the process. VINCI servers for data, applications and virtual sessions are physically located in the VA Automation Center in Austin, Texas. This secure enclave with 20 racks of high-performance servers and 72 terabytes of high-speed data storage has multiple layers of security to prevent data loss. When study data requested through VINCI is approved for use, it is extracted from source databases and placed in SQL tables accessible only to the research team and VA Automation Center OI&T operations personnel.

10.3 Quality Assurance

10.3.1 Training

This study will utilize a Manual of Operations (MOP) and Standard Operating Procedures (SOP) that will contain all training requirements and study procedures/protocols to be used across all study sites. A Regulatory Binder will also be kept throughout the study to organize and track training requirements and milestones. Drs. Ilgen and Lin will be responsible for ensuring the standardization of procedures among staff and investigators and the overall protection of human subjects enrolled in this study. The Project Managers will aid in the oversight of project personnel, the organization of project meetings, and training staff on human subject's research. Communication among staff and investigators will be facilitated by a combination of in-person, phone, and computer-aided (e.g., Zoom, Microsoft Teams, etc.) meetings organized by the Project Managers. Based on previous experience with managing staff on clinical trial projects, we have developed a productive organizational flow for project meetings, participant risk assessment, and overall human subjects and data safety. All identified investigators and staff on the proposed project will have appropriate training in the protection of human subjects as required by NIH and local sites and only those with training certificates will be able to interact with participants and access participant data.

In previous studies, we have operationalized training in a systematic way. All staff will attend an orientation at their employment location and complete the appropriate mandatory trainings and necessary requirements to be approved as staff on the project's IRB application before they may interact with any participants. For specifics on therapist or research staff session training, please see section 5.1 "Conditions, Administration, and Duration" above. All staff will also be required to do the following tasks:

(a) Read grant application (as applicable), study protocol, IRB application
(b) Read selected articles or other materials related to the target study population
(c) Read project specific Manual of Operations for policies and procedures and participate in associated trainings
(d) Attend Risk Assessment presentations, review risk assessment protocols, role play risk assessments, identify chain of tasks for high risk
(e) Attend IRB related presentations and trainings, including Consenting training

(f) Complete online trainings as assigned (including cash handling procedures)
(g) Review databases and data entry with data manager
(h) Review of recruitment procedures, including general overview, how to identify potential participants, screening recruitment scripts, miss/refusal/exclusion codes, administration procedures
(i) Review of study enrollment procedures including Informed Consent, Randomization, measures administration, etc.

For VA sites, staff who are not hired through the VA will be required to complete the process to become a Without Compensation (WOC) Employee in order to access VA patients and records. A Research Service Without Compensation (WOC) employee is an individual who performs research-related duties without any direct monetary compensation from the Department of Veterans Affairs. Individuals requiring WOC appointments include, but are not limited to, students, university employees, non-paid interns, fellows, residents, other non-VA employees working at VA sites (including personnel on IPA contracts), volunteers, and visiting scientists who are not compensated by the VA for their employment. The Research Service is required to collect and maintain certain personal, professional and education/training information. WOC employees are required to renew their status annually until such time as they leave service. VA computer accounts, including access to the VHA medical record system, CPRS, will not be issued until fingerprinting and a background check have been completed.

10.3.2 Quality Control Committee

As part of their responsibilities, the IMC will be responsible for assessing study progress (including patient confidentiality, recruitment and retention, and data quality and management).

10.3.3 Metrics

All data collection forms will be reviewed for accuracy and completeness following their administration by research staff. Any incomplete forms or questions will be assessed by the research staff member with the participant for clarification if possible to minimize the presence of missing data.

10.3.4 Protocol Deviations

All research study staff will be required to review the study protocol and will be trained on the proper administration and tracking of all study procedures, including what constitutes a protocol deviation. The study will utilize both a Protocol Deviation Tracking Log and the Unanticipated Problem (UP) Form to capture all protocol deviations as required by NCCIH policy. We will follow the best practice recommendations as outlined by the NCCIH for using the log, which includes (1) entering the protocol deviations in the tracking log as they occur, (2) having the PI sign each form after it has been completed or immediately prior to a monitoring visit, (3) maintaining the log in the study Regulatory Binder. All protocol deviations will also require an Unanticipated Problem (UP) form to be complete following the incident which will be reviewed by the project managers and signed by the project PI. Based on the type and severity of the deviation, re-training of staff or other disciplinary actions may be necessary to ensure future protocol compliance.

Major deviations will be reported to the IRB and others (e.g., the program official, the NCCIH clinical director), as required. A summary of all deviations will be provided to the Independent Monitoring Committee as part of their report. We will follow the University of Michigan IRBMED Multi-Site Research Reporting Plan in the reporting of protocol deviations (see 15.2 Appendix B).

10.3.5 Monitoring

Data quality and protocol compliance will be monitored throughout the study in a variety of ways. A full schedule for reviews will be included in the Manual of Procedures (MOP) but will be outlined here. Review of the rate of subject accrual and compliance with inclusion/exclusion criteria will occur monthly during the recruitment phase to ensure that a sufficient number of participants are being enrolled, in keeping with proposed recruitment projections, and that they meet eligibility criteria and fulfill the targeted ethnic diversity goals outlined in the grant proposal (Targeted/Planned Enrollment Table). Accrual reports will be submitted to NCCIH at least every 4 months and included in the IMC annual reports. Data on adherence to the condition protocol will be collected on an ongoing basis during the conduction of the study by research staff and reviewed monthly by the PI/Project Managers. Adherence of participants will be evaluated by the Project Manager. If adherence falls below the expected rate, which might inhibit the ability of the study to test its primary hypotheses, the Project Managers will suggest a conference call for study investigators to discuss methods for improving adherence. Study progress and safety will be reviewed monthly (and more frequently if needed). Progress reports, including patient recruitment, retention/attrition, and AEs will be provided to the Independent Monitoring Committee annually. An Annual Report will be compiled and will include a list and summary of AEs. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to the Independent Monitoring Committee and will be forwarded to the IRB and NCCIH. The IRB and other applicable recipients will review progress of this study on an annual basis.

This project will follow the project Data and Safety Monitoring Plan (DSMP) which will outline the specific ways in which study progress will be monitored. Additionally, according to NCCIH requirements this study will have an Independent Monitoring Committee (IMC) which will be responsible for overseeing study progress and procedures as well as monitoring participant safety outcomes (including AEs and SAEs) throughout the duration of the study. The Project Managers will be responsible for creating and maintain a Regulatory Binder, which will contain the C.V. of all the investigators and research staff. All the investigators and research staff involved in this trial will have completed the required NIH and local site educational programs on protection of human subjects, Good Clinical Practice, and scientific ethics. Documentation of completion will be filed in the Regulatory Binder. The binder will also contain all communications to the IRB, including the initial applications, study protocol, any amendments, annual IRB renewal, IRB approvals, and a summary of adverse events. It will be the responsibility of the Project Managers to maintain and update the Regulatory Binder. The Independent Monitoring Committee's primary responsibilities are to monitor participant safety and assess study progress (including participant

confidentiality, recruitment and retention, and data quality and management). For more information regarding the IMC, please see Section 12. “Committees” below) and the Data and Safety Monitoring Plan.

At project startup, and then once per year, the full project team including investigators and staff, will meet to focus/re-focus to project goals, summarize challenges and successes, and participate in applicable trainings. We find these meetings to be especially productive as a “kick-off” to the start of the project to orient all team members to the aims and timeline of the project. These meetings are ideal for the Co-Investigators to attend to offer specialized training and expertise to the project. These meetings are designed to plan and revisit protocols for human subject safety and to ensure that protocols approved by the Institutional Review Board are being followed. In addition, key study staff members including Drs. Ilgen and Lin, the Project Managers, and Co-Investigators as necessary and available will meet monthly to communicate on issues related to project protocol, measurement design, condition manual development, PPMI and EUC staff training and supervision, recruitment and follow-up strategies, risk management, staffing, and dissemination of project findings. These meetings may occur more frequently during the beginning of the project to study staff plans for recruitment, or as issues with study accrual, retention, or safety arise throughout the study. An IRB coordinator may also join these meetings when issues related to study protocol or participant safety and confidentiality are on the agenda. More urgent issues, such as participant risk, will be immediately discussed between the PI and Project Managers via use of a paging system.

To ensure adherence to study procedures and protocols, the Project Managers will meet on a weekly basis with project staff including Research Assistants and Therapists. We have found that weekly meetings with project staff are beneficial for several reasons, including: 1) maintaining project morale throughout the course of the project, which helps to keep the project team intact and ensure consistent productivity, 2) identifying common challenges among staff and brainstorming solutions (e.g., locating space, communicating with hard-to-reach participants), and 3) communicating project protocol changes that impact the whole team (e.g., changes in recruitment strategy, paperwork, etc.). The Data Manager and Analysts will attend when data-related content is discussed in these meetings. These staff meetings are also used for re-training on participant risk assessment and protection of human subjects including data protection, the informed consent process. The PPMI Therapists will meet with Dr. Ilgen, Dr. Lin, or another specified clinical supervisor biweekly for intervention-specific supervision throughout the intervention condition delivery phase of the project. Dr. Ilgen, Dr. Lin, or another specified clinical supervisor will be responsible for listening to intervention condition session recordings for fidelity to the PPMI manual, project risk protocol, and mastery of overall therapeutic delivery.

The project managers will review consent forms, interviews and other source data including case report and tracking forms for accuracy and completeness. Each review will be documented in the Monitoring Log filed in the Regulatory Binder. Data will be reviewed by random inspection of the completed forms by the project managers and any problems detected will be discussed with the PI. In terms of delivery of the PPMI and EUC conditions, therapists and research staff will receive standardized training in conducting both treatment conditions (for details see Section 5.1 “Conditions, Administration, and Duration above). Adherence to PPMI therapy techniques will be monitored using recordings and individual supervision. If session content drift is observed, the therapist or research staff member will

be retrained.

All source documents including recruitment logs, eligibility forms, CRFs, consent checklists, etc. will be reviewed for quality assurance. The Project Managers will be responsible for guiding the Quality Assurance process, and will complete all quality checks or review the results of quality assurance checks completed by specified staff members. Quality assurance checks will be accomplished in several ways listed below:

Data type	Frequency of review	Reviewer
Subject accrual (including compliance with protocol enrollment criteria)	Monthly	PI, Project Managers
	Annually	IMC
Status of all enrolled subjects, as of date of reporting	Monthly	PI, Project Managers
	Annually	IMC
Data entry quality control checks on 20% of charts	Quarterly	Project Managers
Adherence data regarding study visits and intervention	Monthly	PI, Project Managers
	Annually	IMC
AEs and rates	Monthly	PI, Project Managers
	Annually	IMC
	Annually	NCCIH
SAEs (unexpected and related)	Per occurrence	PI, IMC, NIH/NCCIH,
SAEs (expected or unrelated)	Per Occurrence	PI, Project Managers
	Annually	IMC, NIH/NCCIH
Unanticipated Problems	Monthly	PI, Project Managers
	Per Policy	IRB

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This project will be submitted to the University of Michigan IRBMED for review as a multisite study with IRBMED as the single IRB for all sites except the Ann Arbor VA. The study was granted a *VA Cooperative Research Provision Exception Determination* and therefore research activity at the VA will be reviewed and approved by the VA Ann Arbor IRB. The Exception Determination allows the use of more than one IRB since VAAAHS and UM do not yet have a reliance agreement in place. The overall materials will be reviewed and approved; these will be supplemented by materials that are specific to local sites. This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the University of Michigan IRBMED. All substantive protocol amendments, other than minor administrative changes as defined by the NCCIH Guidance on Changes in Clinical Studies in Active Awards will be submitted in a prospective manner to NCCIH except when necessary to protect the safety, rights, or welfare of subjects. Changes will not be implemented until appropriate IRB approval is obtained.

11.2 Informed Consent Forms

Since this is a multisite project, the consent process for sites covered under the IRBMED will include a two-part consent that will be reviewed with the participant: Part 1 of the consent document is the multisite portion of the consent which describes the study design and procedures; Part 2 of the consent document describes any site specific information that is different from or in addition to the information included in Part 1. Approval of the informed consent documents (both Part 1 and Part 2) will be obtained from the Institutional Review Board at the University of Michigan (who will be serving as the single IRB of record for the multisite project), NCCIH, and any additional regulatory bodies as necessary. Informed consent documents for VHA participants will be approved by the VA Ann Arbor IRB. For the eligibility screening survey, we will obtain a waiver of documentation of informed consent. Participants will be provided with information detailing study procedures (either as part of the electronic consent or verbally over the phone or video chat) and will be presented with an option to agree to participate. For the baseline assessment and subsequent enrollment into the RCT, written or verbal (with waiver of documentation) informed consent will be obtained from all participants before data collection begins. Detailed information on the informed consent process is including in previous sections within this protocol (see Section 4.3 'Study Enrollment Procedures' and Section 6.2.1 'Consenting Procedures'). Approval of the informed consent documents will be obtained from NCCIH and the Institutional Review Board at the University of Michigan. We will also adhere to the Certificate of Confidentiality from NIH.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects. The consent document will include language that states the participant may withdraw consent at any time throughout the course of the study. A consent form describing in detail the study procedures and risks will be given to the subject. 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 and this fact will be documented in the participant's record. The participant will be required to read and review the document or have the document read to him or her. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study. The consent process will be documented in the research record. All consent forms will be stored in locked cabinets in restricted access research space or on a secure server. Individuals who cannot provide voluntary, informed consent will be excluded from participation. Accommodations will be made for individuals with disabilities to allow for study participation. To complete the informed consent process at the end of study participation, study staff will inform the subject when his/her participation has come to an end and will document the discussion in the study record.

11.3 Participant Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover all study information relating to subjects. All project staff will be trained on HIPAA compliance and all requirements for human subject research as established by the University of Michigan Medical School IRB, local sites, and NIH. Every effort will be made to ensure that study data is always confidential, in terms of staff training and data storage, so that data cannot be linked to a particular person. Training of staff will include information about the importance of confidentiality and techniques

to maintain confidentiality of all information reported by research participants. Participants will be informed of the procedures taken to protect their confidentiality. Throughout the study, IRB and HIPAA guidelines will be followed to ensure privacy of patient data. Appropriate procedures will be put in place to minimize this risk and ensure that participants' confidentiality is protected. Unique identification numbers will be assigned to all participants who complete the assessments and the participant code will appear on assessment forms; data forms and assessments will be coded with this number, rather than with a name; participants names and other identifying information will be kept separately from study data on a secure server with restricted access and/or in a locked cabinet in a locked room; the audio recordings of the sessions will be converted into computer files, which will be stored on a secure server with restricted access. All research data will be presented in aggregate form only. Additionally, this research is covered by a Certificate of Confidentiality from the NIH to protect the confidentiality of our participants. Equipment used to record the intervention sessions will be approved as necessary by local sites and potential participants will be asked to explicitly consent to having an audio recording of the session These recordings will not be labelled with any study related information, i.e., study name, study ID number. Recordings will be edited to remove anything that could potentially identify participants, such as specific dates, names or places. Participants may still participate if they choose not to consent to the audio-recording.

The program sessions will take place by telephone or video chat. Study cell phones used to communicate with participants and complete therapy sessions will have strong password protection and Microsoft Company Portal protection, which is required of all mobile devices accessing the U-M network. Company Portal enables safeguards against data compromise, malware, and ransomware and has a user portal to manage devices in case of theft, loss, or forgotten passwords. Participants may choose the video chat platform most convenient for them (e.g., Zoom, , FaceTime or Skype for Business) for assessments, condition sessions or interviews, however, HIPAA compliant platforms (e.g., Zoom) will be recommended and encouraged. Confidentiality will be kept to the degree permitted by the technology being used. If a platform is used which is not affiliated with the University of Michigan (i.e., Facetime), it is possible that a participant could be automatically recorded by the platform – similar to when they use these platforms in everyday life. Although every reasonable effort will be taken, confidentiality during actual remote communication procedures cannot be guaranteed.

During this study, the major potential risk to study participants is violation of confidentiality of qualitative interview and assessment data. The risk of violation of confidentiality exists because participants will be disclosing personal information in assessments and intervention sessions. This risk is related to the damage that could be caused by an inadvertent release of sensitive information (e.g., substance use, medical conditions). Participants will be informed of the procedures taken to protect their confidentiality. There is also a slight risk of psychological discomfort to study participants as a result of being asked personal questions on sensitive topics. Participants may also become anxious or upset during discussions of their thoughts about managing their pain or substance use during the condition sessions and/or the assessments. Study staff will be trained to respond to this emotional distress and to refer participants to appropriate resources, as necessary. All participants will be free to terminate the assessments at any time or refuse to respond to any questionnaire item. All information collected is for research purposes only, and data will be kept in strict confidence. Under the 21st Century Cures Act, this study is covered by a Certificate of Confidentiality from NIH. Drs. Ilgen and Lin will ensure that all relevant IRBMED policies, procedures, and stipulations are being

followed. They will also will be responsible for ensuring that other investigators and project staff adhere to the UM IRBMED policies including: (1) all participants will understand, agree to and provide informed consent for the study before participating; (2) strict adherence to a participant's right to withdraw or refuse to answer questions will be maintained; (3) all interviews and assessments will be confidential and no names will be associated with the interview data; (4) consent forms and identifying information will be kept separate from the actual participant data; (5) all identifying information (consents, tracking data) will be kept locked in a filing cabinet at all times and computer files will be saved with passwords; and (6) participants will be informed, in the consent form, how to contact the PI, the project managers, and the IRBMED office with any questions and/or concerns. Drs. Ilgen and Lin will be responsible for communicating with the IRB, the sponsor, or other regulatory agencies in the event of a breach of confidentiality according to the specified guidelines.

11.4 Study Discontinuation

The study may be discontinued at any time by the University of Michigan or Ann Arbor VA IRBs, the NCCIH, the Independent Monitoring Committee or other government agencies as part of their duties to ensure that research participants are protected. The Independent Monitoring Committee will determine whether the study (or intervention for an individual or study cohort) should continue per protocol, proceed with enhanced monitoring, be further investigated, be discontinued, or be modified and then proceed. Suspension of enrollment (for a particular group, a particular study site or for the entire study) is a potential outcome of a monitoring committee review.

Review of serious, unexpected, and related AEs by the Independent Monitoring Committee, IRB, the sponsor(s), or relevant local regulatory authorities may also result in suspension of further study interventions at a site. The study sponsor(s) retain the authority to suspend additional enrollment and study conditions for the entire study, as applicable. Findings that might trigger a safety review are the number of overall SAEs, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events.

12. COMMITTEES

As per NCCIH guidelines, this project will have an Independent Monitoring Committee (IMC) that will be approved by the PI, NIH and NCCIH, and the University of Michigan Medical School and Ann Arbor VA IRBs. The IMC will have a charter that outlines the responsibilities and membership of the IMC. The primary responsibilities of the IMC are to monitor participant safety and assess study progress (including participant confidentiality, recruitment and retention, and data quality and management). The Committee will be composed of three faculty-members not involved with the project who have expertise in pain treatment trials, substance use disorders, and statistics. The Committee will review the protocol before the study is initiated, with an emphasis on participant safety, and can recommend changes. Once the study begins, the committee will meet annually throughout the study to review data on adverse events, recruitment, and adherence to the protocol. The Committee will convene on an ad hoc basis when immediate safety or study concerns arise. The project PI, project managers, investigators, and designated staff will attend the meeting (as non-voting members) and will be responsible for preparing and presenting data reports related to the study. The Committee will decide on stopping rules for the study, such as stopping because of a significant number of injuries or illnesses that can be attributed to study participation. After each

meeting, the Committee Chair will draft a summary report of the meeting discussions and resulting recommendations, which will be submitted to the local IRB and to NIH at each annual review.

The Independent Monitoring Committee for this study is comprised of Anna Kratz, PhD (Clinical Psychologist), Wyndy Wiitala, PhD (Statistician) and Jeffrey Kullgren, MD (General Internist). Drs. Kratz, Wiitala and Kullgren are not associated with this research project and work independently of the PIs, Dr. Mark Ilgen and Dr. Allison Lin. They are not part of the key personnel involved in this grant. No member of the Committee has collaborated or co-published with the contact PI within the past three years. They are qualified to review the patient safety data generated by this study because of their unique expertise. The CVs of all members of the IMC are included in the Regulatory Binder.

The study team will generate Study Reports for the Independent Monitoring Committee using the NCCIH IMC Report Template. Information in the report will include protocol synopsis, enrollment and subject status, demographics and baseline characteristics, safety summary including adverse events, protocol deviations, quality management and outcomes data. Reports will not provide data on primary or secondary endpoints. Study Report tables will be generated only from aggregate (not by group assignment) baseline and aggregate safety data for the study population.

13. PUBLICATION OF RESEARCH FINDINGS

Results of this study may be reported in journals, publications, or at conferences. Individual participants will not be identified by name, by recognizable photograph, voiceprint, or by any other means without specific consent or authorization from the participant. No information that can be used to identify an individual participant will be released or published unless required by law. Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NCCIH prior to submission.

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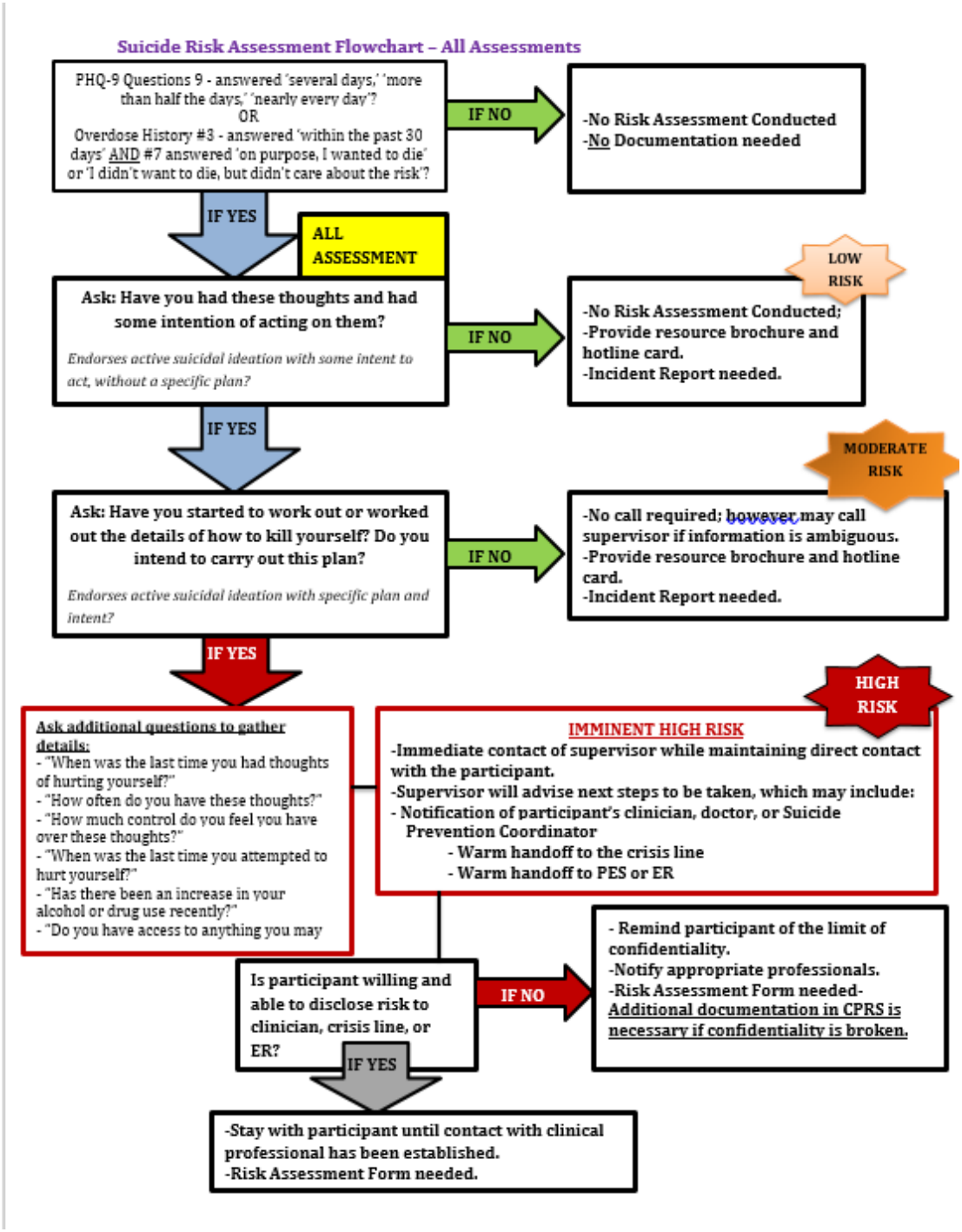
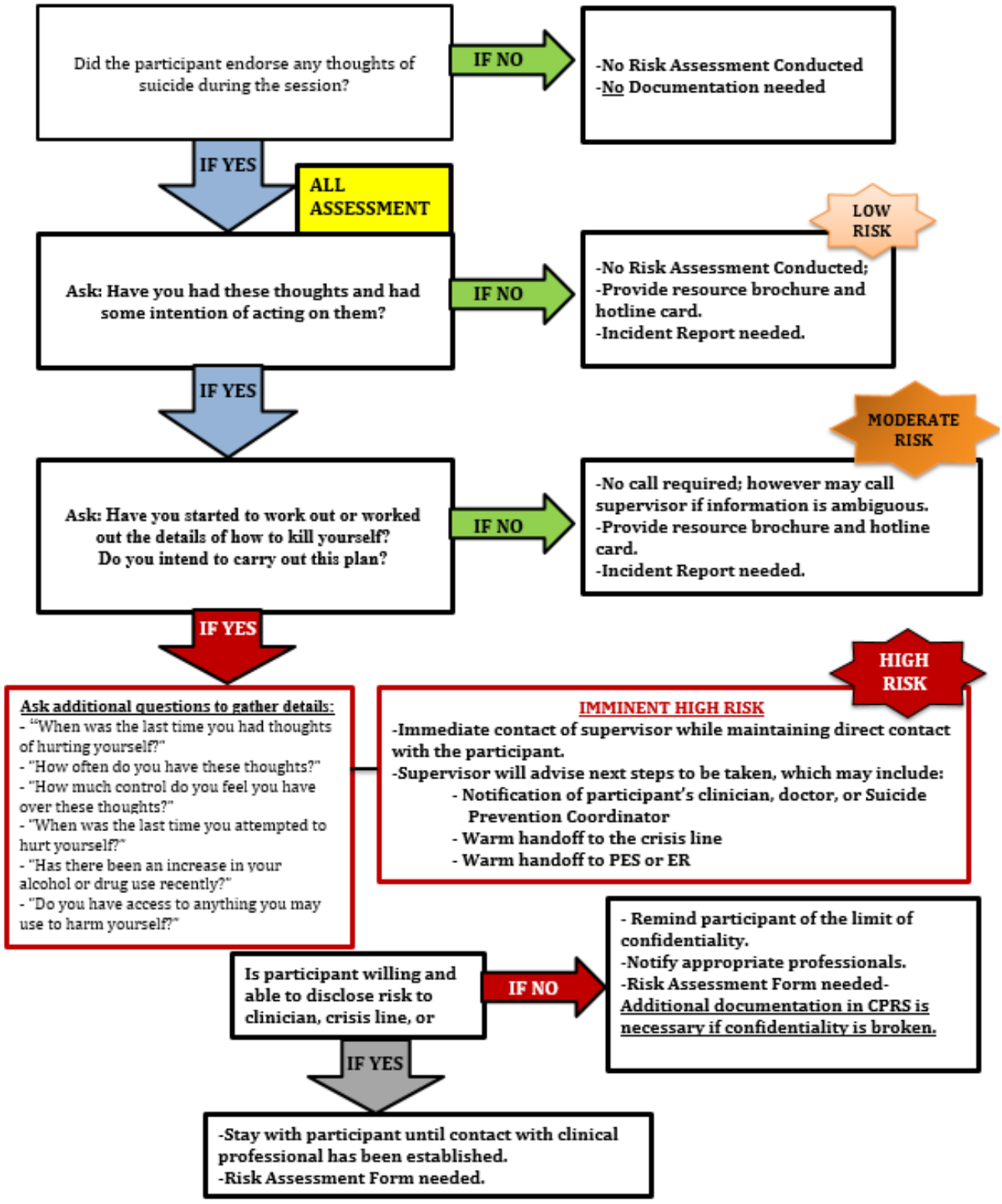
15. SUPPLEMENTS/APPENDICES

15.1 Appendix A: Risk Assessment Flowcharts (suicide, Resource List for overdose, and acute intoxication)

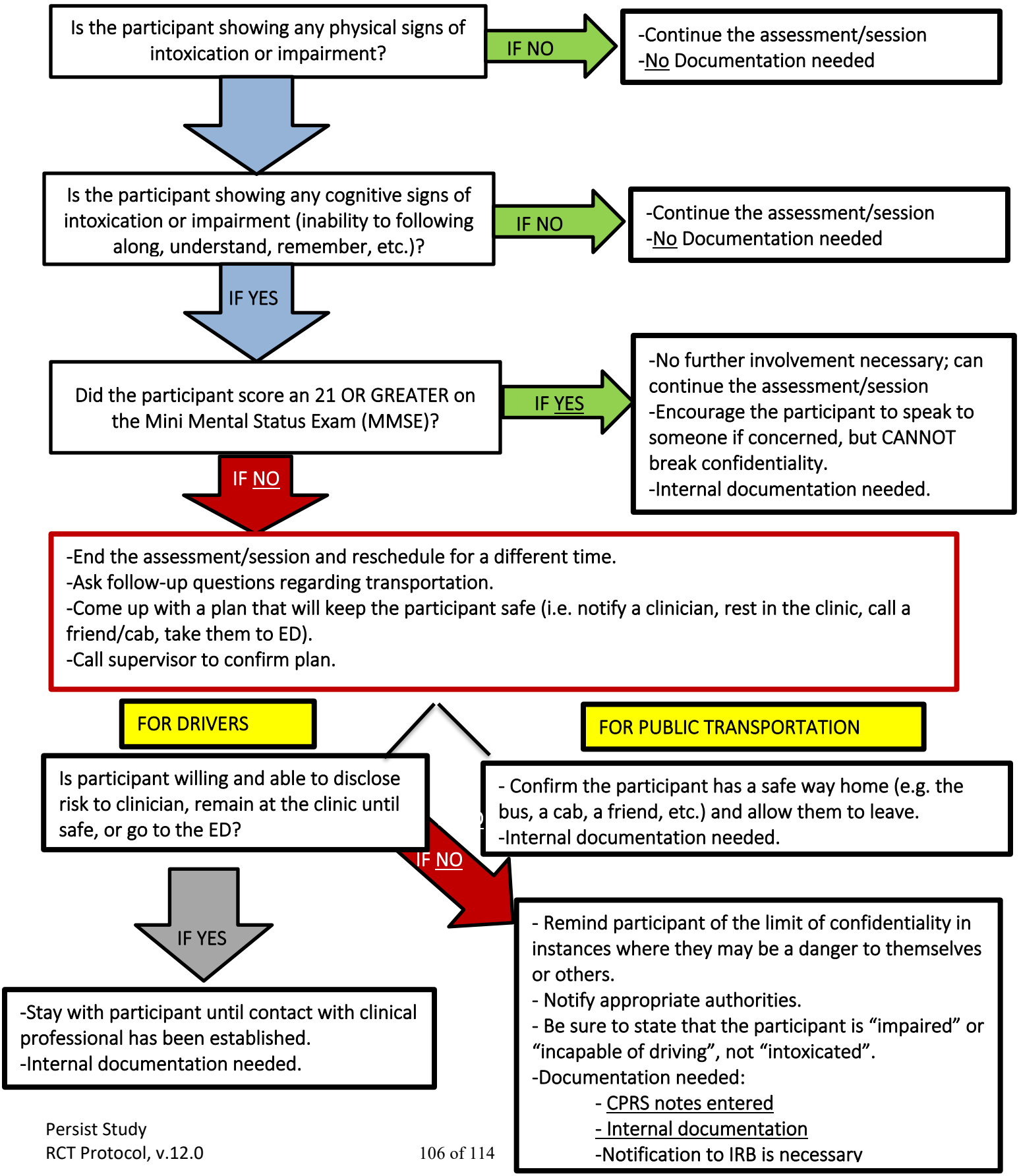
Suicide Risk Assessment Flowchart – All Assessments



Suicide Risk Assessment Flowchart – Therapy session



Acute Intoxication Flowchart



Resource List Brochure

Safe Handing of Medication

- Dispose of all unused or expired medications at a pharmacy or local safe disposal bin
- Keep potentially harmful or addictive medications locked away from children or pets
- Make sure that you or those around you have access to Narcan, a lifesaving medication for opioid overdose. You can purchase Narcan at most pharmacies without a prescription or speak to your doctor about a prescription
- If you feel that you are at risk of relapse, contact your doctor, 911, or a crisis line

SAMHSA Addiction Hotline: 1-800-662-HELP (4357)

Questions? Concerns? Contact us.

734-936-1386

UM-persist-study@med.umich.edu

umpersiststudy.org

Health Information and Resource List

University of Michigan Persist Study

IRBMED: #HUM00166747

Local health resources, safety tips, and medication best practices

Things to think about

Did you know that using drugs and alcohol can...

- Affect your mood and your thinking while using and after using?
- Get you in legal or financial trouble, and hurt your relationships?
- Result in serious injury to you or other people?
- Mess up your chances with a job?
- Increase your risk of getting HIV or STDs?

Warning signs of a problem with drugs or alcohol include:

- Using often
- Advice from a health care provider not to use prescription medication or drink
- Having frequent hangovers or feeling sick when you don't use
- Feeling run-down, depressed, or even suicidal
- Having "blackouts" -- forgetting what you did while using
- Giving up activities or avoiding your friends and family who don't use

Additional Resources

Looking for somewhere to get non-emergency medical care or support? Try these local and national resources:

- SAMHSA Treatment Locator **findtreatment.samhsa.gov**
- Michigan Health and Human Services **www.michigan.gov/mdhhs**
- Support Group Locators **www.verywellmind.com/find-a-support-group-meeting-near-you**

  www.smartrecovery.org
- Mental Health Resources **www.samhsa.com**

  www.mentalhealth.gov
- Harm Reduction / MAT information **www.harmreduction.org**

What to do when you're feeling low:

- Contact a trusted friend, family member, sponsor, or counselor and tell them how you feel.
- Find a nearby recovery group
- Find a healthy way to release anger or other emotions like exercise, writing, or drawing
- Contact the 24/7 suicide hotline or call 911 if you feel unsafe.
- Find a pleasurable activity to distract yourself such as taking a walk or listening to your favorite music.
- Visit the emergency room if you need immediate care.

National Suicide Prevention Line:
1-800-273-8255
For Veterans: press 1
Or Dial or Text 988
UM Crisis Services:
732-936-5900 or 734-996-4747

15.2 Appendix B: University of Michigan IRBMED Multi-Site Research Reporting Plan

MEDICAL SCHOOL
UNIVERSITY OF MICHIGAN

Multi-site Research Reporting Plan

Definitions, Reporting Timeframes, Procedures

REPORTABLE WITHIN 7 DAYS

The following types of events must be reported to the lead site (University of Michigan) study team within 7 calendar days of *becoming aware of the event.*

Unanticipated Problems Involving Risks to Human Subjects or Others: an actual incident, experience, or outcome that warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others. The following criteria must be met:

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

Non-compliance: The failure of a person or organization to act in accordance with the requirements of a law, regulation, policy, or the requirements and/or determination of an IRB. *Major* protocol deviations that may adversely impact safety of participants, or impact integrity/validity of the data are considered non-compliance (such as dosage errors/intervention errors, consent process deviations, deliberate procedural deviations, and accidental procedural deviations)

Continuing non-compliance: Noncompliance that recurs after an investigator has been notified of a similar or related noncompliance concern pertaining to one or more protocols.

Serious non-compliance: Non-compliance that, in the judgment of the IRB, materially increases the risks or causes substantive harm to research participants or materially compromises the rights or welfare of participants including consideration of the following:

1. Harm to participants;
2. Exposure of participants to a significant risk of substantive harm;
3. Compromised privacy and confidentiality of participants;
4. Willful or knowing research misconduct on the part of the investigator;
5. A violation of ethical principles for human research; or
6. Damage caused to the scientific integrity of the data collected.

Complaints: Complaints from any individual related to participant safety, study conduct, or study related materials.

Accident/Incident: Accidents/Incidents involving participants, their data, biospecimens or facilities associated with the research (e.g., breach of confidentiality, loss of research data or biospecimens).

Subject Incarceration: Incarceration of a participant when the research was not previously approved for the enrollment of prisoners under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.

Oversight Reports: Reports of internal or external audits; study holds or suspensions that are not built into the study design and affect the local site only. Reports of monitoring (such as Data Safety Monitoring) outcomes that have concerns of subject safety or suggested revision of study materials.

Subject Withdrawal: Withdrawal due to safety reasons.

Pertinent publication/public announcement: Information affecting the risk/benefit ration of the study or information affecting subjects' willingness to participate in the research.

IRB Approval Lapse: Report of any study activity during the lapse in approval (this can happen if a site does not get information to lead site in time for the submission of the continuing review).

REPORTABLE AT CONTINUING REVIEW

The following types of events must be reported to the lead site (University of Michigan) study team at the next scheduled continuing review.

Site Status Reports: Site enrollment closed and/or completed interaction/intervention notifications without safety or regulatory concerns

Subject Withdrawal: Withdrawal of a subject due to PI discretion, subject discretion/request or other reasons, such as meeting protocol stopping rules.

15.3 Appendix C: UScreen Drug Test Insert

Using the UScreen Cup Drug Test

Step 1

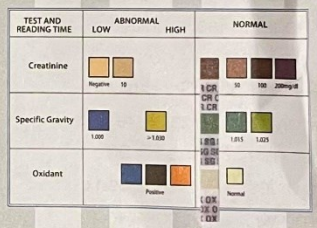
Have the donor provide a specimen and return the cup to the collector. Check the temperature strip to assure valid specimen.

Step 2

Replace the cap and set the cup on a flat surface and remove label. If test cup is equipped with an optional adulterant test strip, please replace cap and proceed to Step 3 prior to Step 4. If not, proceed to Step 4.

Step 3

If equipped, place the slot on the adulterant color guide over the adulterant strip on the cup. If any of the test pads match any of the colors on the left, adulteration is indicated. In this case, collect a new specimen in a new cup and retest.



Step 4

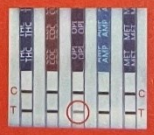
Interpret results. Negative results can be interpreted as soon as all test lines are visible. Do not interpret positive results before 5 minutes.

Reading the Results

Read the results when all upper "Control" or "C" lines have appeared. Negative results can be read as soon as all "Test" or "T" lines are visible. (Wait 5 minutes to determine a Positive Result)

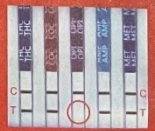
Negative

A negative result is indicated by the presence of the lower "Test" or "T" Line for each designated drug.



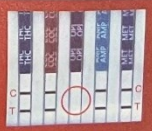
Negative

The presence of even a very light "Test" or "T" Line indicates a negative result.



Positive

A positive result is indicated by the absence of the lower "Test" or "T" Line for a specific drug. Wait 5 minutes to determine a positive result.



Invalid

An invalid result is indicated by the absence of the upper "Control" or "C" Line . If this occurs run a second test.

UScreen®

DRUG TEST CUP

Catalogue No. See Box label

CLIA CATEGORIZATION: WAIVED

URINE SCREENING TEST RESULTS IN 5 MINUTES

The UScreen Drugs of Abuse Cup tests for the possible use of Marijuana (THC), Cocaine (COC), Amphetamine (AMP), Methamphetamine (MET), Methylenedioxymethamphetamine - ecstasy (MDMA), Morphine (MOP/OPI300), Morphine 2000 (OPI), Barbiturates (BAR), Benzodiazepines (BZO), Methadone (MTD), Phencyclidine (PCP), Oxycodone, (OXY), Tri-cyclic Antidepressants (TCA) and Buprenorphine(BUP).

The Uscreen Drugs of Abuse Cup is a rapid, screening test for the qualitative detection of multiple drugs in human urine at specified cut off levels.
For Healthcare professionals including professionals at point of care sites.
For in vitro diagnostic use only.

WHAT IS THE USCREEN DRUGS OF ABUSE CUP?

The UScreen Drugs of Abuse Cup is an immuno-chromatographic assay for the qualitative determination of the presence of drugs listed in the table below. The test you purchased may test for any combination of drugs listed.

WHAT IS THE CUT-OFF VALUE AND APPROXIMATE DETECTION TIME?

Drug(Identifier)	Cut-off level	Minimum detection time	Maximum detection time
Marijuana (THC)	50 ng/mL	2 hours	Up to 5+ days
Cocaine (COC)	300 ng/mL	1-4 hours	2-4 days
Amphetamine (AMP)	1000 ng/mL	2-7 hours	2-4 days
Methamphetamine (MET)	1000 ng/mL	2-7 hours	2-4 days
Morphine (MOP/OPI300)	300 ng/mL	2 hours	2-3 days
Morphine 2000 (OPI)	2000 ng/mL	2 hours	2-3 days
Methylenedioxymethamphetamine (MDMA)	500 ng/mL	2-7 hours	2-4 days
Barbiturates (BAR)	300 ng/mL	2-4 hours	1-3 weeks
Benzodiazepines (BZO)	300 ng/mL	2-7 hours	1-4 days
Methadone (MTD)	300 ng/mL	3-8 hours	1-3 days
Oxycodone (OXY)	100 ng/mL	1-3 hours	1-2 days
Phencyclidine (PCP)	25 ng/mL	4-6 hours	7-14days
Tri-cyclic Antidepressants (TCA)	1000 ng/mL	8-12hours	2-7 days
Buprenorphine(BUP)	10 ng/mL	4 hours	1-3 days

WARNINGS AND PRECAUTIONS

- This kit is for external use only
- Discard after first use. The test cannot be used more than once
- Keep out of the reach of children
- Do not use if pouch is punctured or not sealed
- Do not use test kit beyond expiration date
- Do not read results after 5 minutes

MATERIALS PROVIDED

- 25 Test devices, one test cup per pouch. Each pouch contains a test cup with integrated test card
- Desiccant Pouch - Remove desiccant from cup. The desiccant is for storage purposes only.
- One (1) Instruction Sheet
- One (1) Adulteration color comparison chart for interpretation of adulteration test results (if equipped)
- 25 Security seals (if Provided)

STORAGE AND STABILITY

- Store at 39 ~ 86 °F (4 ~ 30 °C) in the sealed pouch up to the expiration date.
- Keep away from direct sunlight, moisture and heat.
- DO NOT FREEZE.

PRINCIPLE

UScreen Drugs of Abuse Cup is a competitive immunoassay that is used to screen for the presence of various drugs in urine. It is a chromatographic absorbent device in which drugs in a urine sample competitively combine to a limited number of drug monoclonal antibody (mouse) conjugate binding sites.

When the test is activated, the urine is absorbed into each test strip by capillary action, mixes with the respective drug monoclonal antibody conjugate, and flows across a pre-coated membrane. When the drug levels within the urine sample is below the detection level of the test, respective drug monoclonal antibody conjugate binds to the respective drug-protein conjugate immobilized in the Test Region (T) of the test strip. This produces a colored Test line in the Test Region (T) of the strip that regardless of its intensity indicates a negative test result.

When the sample drug levels are at or above the detection level of the test, the free drug in the sample binds to the respective drug monoclonal antibody conjugate, preventing the respective drug monoclonal antibody conjugate from binding to the respective drug-protein conjugate immobilized in the Test Region (T) of the device. This prevents the development of a distinct colored band in the test region, indicating a preliminary positive result.

To serve as a procedure control, a colored line will appear at the Control Region (C), of each strip, if the test has been performed properly.

SPECIMEN COLLECTION AND PREPARATION

WHEN TO COLLECT URINE FOR THE TEST?
Collect the urine sample after the minimum detection time following suspected drug use. Urine collection time is very important in detecting any drug of abuse. Each drug is cleared by the body and is detected in the urine at different times and rates. Please refer to the section "WHAT IS THE CUT-OFF VALUE AND APPROXIMATE DETECTION TIMES?" contained within this package insert, to determine the minimum/maximum detection times, and cut-off level for each drug.

HOW TO COLLECT URINE?
1. Remove a test cup from the foil pouch by tearing at the notch. Use it as soon as possible. Instruct the donor to remove the cap from the test cup, and void directly into the test cup. Instruct the donor to fill the cup to the 30 mL mark. It is acceptable to collect an extra urine sample.
2. Immediately read the temperature to verify that the urine temperature is within the acceptable range 90-100°F (32-38°C).

HOW TO PERFORM THE TEST?

Test must be performed at room temperature, 65-86°F (18-30°C).
1. After the urine has been collected, tighten lid, and place the test cup on a flat surface.
2. Read the temperature immediately to verify that the urine temperature is within the acceptable range 90 – 100°F (32 – 38°C)
3. Remove Cup label, and verify that adulterant pad colors are within acceptable range according to adulteration guide (if your cup is equipped with specimen validity/adulterant pads.)
4. Remove the label and read the results. Wait 5 minutes to determine a positive result.
5. **Do not read results after 5 minutes.** *Results after more than 5 minutes may be not accurate and should not be read.*

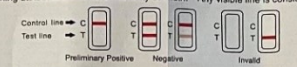
READING THE RESULTS

Preliminary positive (+)
A rose-pink band is visible in each control region. If no color band appears in the appropriate test "T" region, a preliminary positive result is indicated for the corresponding drug of that specific test zone.

Negative (-)
If a rose-pink band is visible in each control region and the appropriate test "T" region, it indicates that the concentration of the corresponding drug of that specific test zone is absent or below the detection limit of the test.

Invalid
If a color band is not visible in the control "C" region or a color band is only visible in the test "T" region, the test is invalid. Another test should be opened and run to re-evaluate the specimen. If test still provides an invalid result, please contact the distributor from whom you purchased the product. When calling, be sure to provide the lot number of the test.

Note: There is no meaning attributed to line color intensity or width. Any visible line is considered to be a line.



Certain lines may appear lighter or thinner than other lines. ANY COLORED LINE VISIBLE IN THE TEST "T" REGION, NO MATTER HOW DARK OR FAINT, SHOULD BE INTERPRETED AS A **NEGATIVE** RESULT. (IMPORTANT: This assay provides only a preliminary analytical test result. A more specific alternative chemical method must be used in order to obtain a confirmed analytical result. Gas Chromatography/Mass Spectrometry (GC/MS) is the preferred confirmatory method. Clinical consideration and professional judgment should be applied to any drug test result, particularly when preliminary positive results are indicated.)

What Is A False Positive Test?
The definition of a false positive test would be an instance where a substance is identified incorrectly by UScreen Drugs of Abuse Cup. The most common causes of a false positive test are cross reactants. Certain foods, medicines, diet plan drugs, and nutritional supplements may cause a false positive test result with this product.

What Is A False Negative Test?
The definition of a false negative test is that the initial drug is present but isn't detected by UScreen Drugs of Abuse Cup. Diluted or adulterated urine specimens may cause a false negative result.

TEST LIMITATIONS

1. This test has been developed for testing urine samples only. No other fluids have been evaluated. DO NOT use this device to test substances other than urine.
2. Adulterated urine samples may produce erroneous results. Strong oxidizing agents such as bleach (hypochlorite) can oxidize drug analytes. If a sample is suspected of being adulterated, obtain a new sample in a different, unused, cup.
3. This test is a qualitative screening assay. It is not designed to determine the quantitative concentration of drugs or the level of intoxication.

ASSISTANCE

If you have any questions regarding the use of this product, please contact US Diagnostics 888-669-4337.

SUMMARY

Amphetamine/Methamphetamine **(AMP/MET)** and their metabolites are potent central nervous system stimulants. Acute doses induce euphoria, alertness, sense of increased energy and power. Responses from chronic use can include anxiety, paranoia, psychotic behavior, cardiac dysrhythmias. Methamphetamine and amphetamine are excreted in the urine as the unchanged drug along with deaminated or hydroxylated derivatives. Methamphetamine also metabolizes to amphetamine in the body. As a result, urine specimens from most methamphetamine users contain both the unchanged parent drug and the amphetamine metabolite.

Barbiturates **(BAR)** are classified as central nervous system depressants. These products produce a state of intoxication that is similar to alcohol intoxication. Symptoms include slurred speech, loss of motor coordination and impaired judgment. Depending on the dose, frequency, duration of use, and tolerance, physical dependency and psychological dependency can occur. Barbiturates are taken orally or by intravenous and intramuscular injections. Members of the barbiturate drug class typically excrete in urine as parent compound and metabolites.

Benzodiazepines **(BZO)** are central nervous system (CNS) depressants commonly prescribed for the short-term treatment of anxiety and insomnia. In general, benzodiazepines act as hypnotics in high doses, as anxiolytics in moderate doses, and as sedatives in low doses. The use of benzodiazepines can result in drowsiness and confusion. Psychological and physical dependence on benzodiazepines can develop if high doses of the drug are given over a prolonged period. Benzodiazepines are taken orally, or by intramuscular or intravenous injection, and are extensively oxidized in the liver to metabolites. Most benzodiazepines are excreted in the urine as conjugates and metabolites.

Cocaine **(COC)** is a potent central nervous system stimulant and a local anesthetic found in the leaves of the coca plant. The psychological effects induced by using cocaine are euphoria, confidence and sense of increased energy. These psychological effects are accompanied by increased heart rate, dilation of the pupils, fever, tremors and sweating. Cocaine is excreted in the urine primarily as benzoylecgonine in a short period of time. Benzoylecgonine has a biological half-life of 5 to 8 hours, which is much longer than that of cocaine (0.5 to 1.5 hour), and can be generally detected for 24 to 60 hours after cocaine use or exposure.

Methylenedioxymethamphetamine **(MDMA)** is classified as both a stimulant and a hallucinogen. Like methamphetamine, adverse effects of 3,4-methylenedioxymethamphetamine use include jaw clenching, teeth grinding, dilated pupils, perspiring, anxiety, blurred vision, vomiting, and increased blood pressure and heartrate. Over dose of 3,4-methylenedioxymethamphetamine may cause heart failure or extreme heat stroke. 3,4-methylenedioxymethamphetamine is taken orally in tablets or capsules and excreted in urine as parent compound and metabolizes including methylenedioxyamphetamine (MDMA).

Methadone **(MTD)** is a synthetic analgesic drug originally used for the treatment of narcotic addiction and pain management. The psychological effects induced by using methadone are analgesia, sedation, and respiratory depression. Overdose of methadone may cause coma or even death. Methadone is taken orally or intravenously and is metabolized in the liver and has a biological half-life of 15-60 hours.

Opiates **(OPI/MOP/OPI300)** such as heroin, morphine, and codeine, are central nervous system (CNS) depressants. The use of opiates at high doses produces euphoria and release from anxiety. Physical dependence is apparent in users and leads to depressed coordination, disrupted decision making, decreased respiration, hypothermia and coma. Heroin is quickly metabolized to 6-acetylmorphine (6-AM), morphine, and morphine glucuronide. Codeine also partially metabolizes to morphine and morphine glucuronide. Thus, the presence of morphine or morphine glucuronide in the urine can indicate heroin, morphine, and/or codeine use.

Oxycodone **(OXY)** is a semi-synthetic opioid with a structure similar to codeine. It produces potent euphoria, analgesic and sedative effects, and has a dependence liability similar to morphine. Oxycodone is most often administered orally and is metabolized by demethylation to noroxycodone and oxymorphone followed by glucuronidation. The window of detection for oxycodone in urine is expected to be similar to that of other opioids such as morphine.

Phencyclidine **(PCP)**, commonly known as "angel dust" and "crystal cyclone," is an arylcyclohexylamine that was originally used as an anesthetic agent and a veterinary tranquilizer. The drug is abused by oral or nasal ingestion, smoking, or intravenous injection. It produces hallucinations, lethargy, disorientation, loss of coordination, trance-like ecstatic states, a sense of euphoria and visual distortions. It is well absorbed following all routes of administration. Unchanged PCP is excreted in urine in moderate amounts (10% of the dose).

Marijuana **(THC)** is generally accepted to be the principle active component in marijuana. When ingested or smoked, it produces euphoric effects. Abusers exhibit central nervous system effects, altered mood and sensory perceptions, loss of coordination, impaired short-term memory, anxiety, paranoia, depression, confusion, hallucinations, and increased heartrate. The primary metabolite of marijuana excreted in the urine is 11-nor-Δ-9-tetrahydrocannabinol-9-carboxylic acid. The elimination of THC and its metabolites in urine is highly dependent on the frequency of drug use and physiology of the user.

Tricyclic Antidepressants **(TCA)** have been prescribed for depression and compulsive disorders. Because of the possibility of causing serious cardiac complications, TCAs can be lethal if misused at high doses. TCAs are taken orally or sometimes by injection. TCAs and their metabolites are excreted in urine (mostly in the form of metabolites) for up to ten days.

Buprenorphine **(BUP)** is a potent analgesic often used in the treatment of opioid addiction. The drug is sold under the trade names Subutex™, Buprenex™, Temgesic™ and Suboxone™, all of which contain Buprenorphine HCl alone or in combination with Naloxone HCl. Therapeutically, Buprenorphine is used as a substitution treatment for opioid addicts. A substitution treatment is a form of medical care offered to opiate addicts (primarily heroin addicts) based on a similar or identical substance to the drug normally used. In substitution therapy, Buprenorphine is as effective as Methadone but demonstrates a lower level of physical dependence. The plasma half-life of Buprenorphine is 2-4 hours. While complete elimination of a single-dose of the drug can take as long as 6 days, the detection window for the parent drug in urine is thought to be approximately 3 days.

QUALITY CONTROL

Users should follow the appropriate federal, state, and local guidelines concerning the frequency of assaying external quality control materials.
Though there is an internal procedural control line in the test device of Control region, the use of external controls is strongly recommended as good laboratory testing practice to confirm the test procedure and to verify proper test performance. Positive and negative control should give the expected results. When testing the positive and negative control, the same assay procedure should be adopted.

PERFORMANCE CHARACTERISTICS

Accuracy
1120 (eighty of each drug) clinical urine specimens were analyzed by GC-MS and by each corresponding UScreen drug of abuse Test. Each UScreen test was read by three viewers. Samples were divided by concentration into five categories: drug-free, less than half the cutoff, near cutoff negative, near cutoff positive, and high positive. Results were as follows:

Drug Test	UScreen Result		Drug Free	Less than half the cutoff concentration by GC/MS analysis	Near Cutoff Negative (Between 50% below the cutoff and the cutoff concentration)	Near Cutoff Positive (Between the cutoff and 50% above the cutoff concentration)	High Positive greater than 50% above the cutoff concentration)	%Agreement with GC/MS (95%CI)
AMP	Viewer A	+	0	0	2	11	29	100% (84.5% - 100%)
		-	10	18	10	0	0	95% (79.5% - 100%)
	Viewer B	+	0	0	2	11	29	100% (84.5% - 100%)
		-	10	18	10	0	0	95% (79.5% - 100%)
	Viewer C	+	0	0	1	11	29	100% (84.5% - 100%)
		-	10	18	11	0	0	97.5% (82% - 100%)
BAR	Viewer A	+	0	0	2	20	20	100% (84.5% - 100%)
		-	10	10	18	0	0	95% (79.5% - 100%)
	Viewer B	+	0	0	2	20	20	100% (84.5% - 100%)
		-	10	10	18	0	0	95% (79.5% - 100%)
	Viewer C	+	0	0	1	20	20	100% (84.5% - 100%)
		-	10	10	19	0	0	97.5% (82% - 100%)
BZO	Viewer A	+	0	0	1	20	20	100% (84.5% - 100%)
		-	10	10	19	0	0	97.5% (82% - 100%)
	Viewer B	+	0	0	1	20	20	100% (84.5% - 100%)
		-	10	10	19	0	0	97.5% (82% - 100%)
	Viewer C	+	0	0	2	20	29	100% (84.5% - 100%)
		-	10	10	18	0	0	95% (79.5% - 100%)
COC	Viewer A	+	0	0	1	11	29	100% (84.5% - 100%)
		-	10	10	19	0	0	97.5% (82% - 100%)
	Viewer B	+	0	0	2	11	29	100% (84.5% - 100%)
		-	10	10	18	0	0	95% (79.5% - 100%)
	Viewer C	+	0	0	2	11	29	100% (84.5% - 100%)
		-	10	10	18	0	0	95% (79.5% - 100%)
THC	Viewer A	+	0	0	2	18	22	100% (84.5% - 100%)
		-	10	12	16	0	0	95% (79.5% - 100%)
	Viewer B	+	0	0	1	18	22	100% (84.5% - 100%)
		-	10	12	17	0	0	97.5% (82% - 100%)
	Viewer C	+	0	0	1	18	22	100% (84.5% - 100%)
		-	10	12	17	0	0	97.5% (82% - 100%)
MET	Viewer A	+	0	0	1	20	20	100% (84.5% - 100%)
		-	10	16	13	0	0	97.5% (82% - 100%)
	Viewer B	+	0	0	2	20	20	100% (84.5% - 100%)
		-	10	16	12	0	0	95% (79.5% - 100%)
	Viewer C	+	0	0	1	20	20	100% (84.5% - 100%)
		-	10	16	13	0	0	97.5% (82% - 100%)
MDMA	Viewer A	+	0	0	2	20	29	100% (84.5% - 100%)
		-	10	10	18	0	0	95% (79.5% - 100%)
	Viewer B	+	0	0	2	20	20	100% (84.5% - 100%)
		-	10	10	18	0	0	95% (79.5% - 100%)
	Viewer C	+	0	0	1	20	20	100% (84.5% - 100%)
		-	10	10	19	0	0	97.5% (82% - 100%)
MOP /OPI300	Viewer A	+	0	0	1	20	20	100% (84.5% - 100%)
		-	10	19	10	0	0	97.5% (82% - 100%)
	Viewer B	+	0	0	2	20	20	100% (84.5% - 100%)
		-	10	19	9	0	0	95% (79.5% - 100%)
	Viewer C	+	0	0	1	20	20	100% (84.5% - 100%)
		-	10	19	10	0	0	97.5% (82% - 100%)
MTD	Viewer A	+	0	0	2	19	21	100% (84.5% - 100%)
		-	10	12	16	0	0	95% (79.5% - 100%)
	Viewer B	+	0	0	1	19	21	100% (84.5% - 100%)
		-	10	12	17	0	0	97.5% (82% - 100%)
	Viewer C	+	0	0	2	19	21	100% (84.5% - 100%)
		-	10	12	16	0	0	95% (79.5% - 100%)
OPI	Viewer A	+	0	0	1	18	22	100% (84.5% - 100%)
		-	10	20	9	0	0	97.5% (82% - 100%)
	Viewer B	+	0	0	1	18	22	100% (84.5% - 100%)
		-	10	20	9	0	0	97.5% (82% - 100%)
	Viewer C	+	0	0	1	18	22	100% (84.5% - 100%)
		-	10	20	9	0	0	97.5% (82% - 100%)
PCP	Viewer A	+	0	0	2	18	22	100% (84.5% - 100%)
		-	10	13	15	0	0	95% (79.5% - 100%)
	Viewer B	+	0	0	2	18	22	100% (84.5% - 100%)
		-	10	13	15	0	0	95% (79.5% - 100%)
	Viewer C	+	0	0	2	18	22	100% (84.5% - 100%)
		-	10	13	15	0	0	95% (79.5% - 100%)
TCA	Viewer A	+	0	0	1	10	30	100% (84.5% - 100%)
		-	10	19	10	0	0	97.5% (82% - 100%)
	Viewer B	+	0	0	1	10	30	100% (84.5% - 100%)
		-	10	19	10	0	0	97.5% (82% - 100%)
	Viewer C	+	0	0	1	10	30	100% (84.5% - 100%)
		-	10	19	10	0	0	97.5% (82% - 100%)

OXY	Viewer A	+	0	0	2	19	21	100% (84.5% - 100%)
		-	10	20	8	0	0	95% (79.5% - 100%)
	Viewer B	+	0	0	2	19	21	100% (84.5% - 100%)
		-	10	20	8	0	0	95% (79.5% - 100%)
	Viewer C	+	0	0	1	19	21	100% (84.5% - 100%)
		-	10	20	9	0	0	97.5% (82% - 100%)
BUP	Viewer A	+	0	0	1	16	24	100% (84.5% - 100%)
		-	10	18	11	0	0	97.5% (82% - 100%)
	Viewer B	+	0	0	1	16	24	100% (84.5% - 100%)
		-	10	18	11	0	0	97.5% (82% - 100%)
	Viewer C	+	0	0	1	16	24	100% (84.5% - 100%)
		-	10	18	11	0	0	97.5% (82% - 100%)

Precision and Sensitivity

To investigate the precision and sensitivity, each drug sample was analyzed at the following concentrations: cutoff - 100%, cutoff - 75%, cutoff - 50%, cutoff - 25%, cutoff, cutoff +25%, cutoff + 50%, cutoff + 75% and the cutoff + 100%. All concentrations were confirmed with GC-MS. The study was performed 2 runs /day and lasted 25 days using three different lots of the corresponding UScreen drugs of abuse test. In total, 3 operators participated in the study of the corresponding UScreen drugs of abuse test. Each of the 3 operators tested 2 aliquots at each concentration for each lot per day (2 runs /day), for a total of 50 determinations per concentration per lot of the corresponding UScreen drugs of abuse test.

Drug test	Approximate concentration of sample (ng/mL)	Number of determinations per lot	Result (Negative/Positive) Lot 1	Lot 2	Lot 3
AMP	0	50	50/0	50/0	50/0
	250	50	50/0	50/0	50/0
	500	50	50/0	50/0	50/0
	750	50	50/0	50/0	50/0
	1000	50	5/45	5/45	4/46
	1250	50	0/50	0/50	0/50
	1500	50	0/50	0/50	0/50
	1750	50	0/50	0/50	0/50
	2000	50	0/50	0/50	0/50
BAR	0	50	50/0	50/0	50/0
	75	50	50/0	50/0	50/0
	150	50	50/0	50/0	50/0
	225	50	50/0	50/0	50/0
	300	50	7/43	5/45	5/45
	375	50	0/50	0/50	0/50
	450	50	0/50	0/50	0/50
	525	50	0/50	0/50	0/50
	600	50	0/50	0/50	0/50
BZO	0	50	50/0	50/0	50/0
	75	50	50/0	50/0	50/0
	150	50	50/0	50/0	50/0
	225	50	50/0	50/0	50/0
	300	50	7/43	6/44	5/45
	375	50	0/50	0/50	0/50
	450	50	0/50	0/50	0/50
	525	50	0/50	0/50	0/50
	600	50	0/50	0/50	0/50
COC	0	50	0/50	0/50	0/50
	75	50	50/0	50/0	50/0
	150	50	50/0	50/0	50/0
	225	50	50/0	50/0	50/0
	300	50	5/45	5/45	5/45
	375	50	0/50	0/50	0/50
	450	50	0/50	0/50	0/50
	525	50	0/50	0/50	0/50
	600	50	0/50	0/50	0/50
THC	0	50	50/0	50/0	50/0
	12.5	50	50/0	50/0	50/0
	25.0	50	50/0	50/0	50/0
	37.5	50	50/0	50/0	50/0
	50.0	50	5/45	6/44	5/45
	62.5	50	0/50	0/50	0/50
	75.0	50	0/50	0/50	0/50
	87.5	50	0/50	0/50	0/50
	100.0	50	0/50	0/50	0/50
MET	0	50	50/0	50/0	50/0
	250	50	50/0	50/0	50/0
	500	50	50/0	50/0	50/0
	750	50	50/0	50/0	50/0
	1000	50	4/46	5/45	5/45
	1250	50	0/50	0/50	0/50
	1500	50	0/50	0/50	0/50
	1750	50	0/50	0/50	0/50
	2000	50	0/50	0/50	0/50
MDMA	0	50	50/0	50/0	50/0
	125	50	50/0	50/0	50/0
	250	50	50/0	50/0	50/0
	375	50	50/0	50/0	50/0
	500	50	6/44	5/45	6/44
	625	50	0/50	0/50	0/50
	750	50	0/50	0/50	0/50
	875	50	0/50	0/50	0/50
	1000	50	0/50	0/50	0/50
MOP/OPI300	0	50	50/0	50/0	50/0
	75	50	50/0	50/0	50/0
	150	50	50/0	50/0	50/0
	225	50	50/0	50/0	50/0
	300	50	5/45	6/44	5/45
	375	50	0/50	0/50	0/50
	450	50	0/50	0/50	0/50
	525	50	0/50	0/50	0/50
	600	50	0/50	0/50	0/50
MTD	0	50	50/0	50/0	50/0
	75	50	50/0	50/0	50/0
	150	50	50/0	50/0	50/0
	225	50	50/0	50/0	50/0
	300	50	6/44	4/46	5/45
	375	50	0/50	0/50	0/50
	450	50	0/50	0/50	0/50
	525	50	0/50	0/50	0/50
	600	50	0/50	0/50	0/50
OPI	0	50	50/0	50/0	50/0
	500	50	50/0	50/0	50/0
	1000	50	50/0	50/0	50/0
	1500	50	50/0	50/0	50/0
	2000	50	5/45	5/45	6/44
	2500	50	0/50	0/50	0/50
	3000	50	0/50	0/50	0/50
	3500	50	0/50	0/50	0/50
	4000	50	0/50	0/50	0/50
PCP	0	50	50/0	50/0	50/0
	6.25	50	50/0	50/0	50/0
	12.5	50	50/0	50/0	50/0
	18.75	50	50/0	50/0	50/0
	25	50	5/45	4/46	5/45
	31.25	50	0/50	0/50	0/50
	37.5	50	0/50	0/50	0/50
	43.75	50	0/50	0/50	0/50
	50	50	0/50	0/50	0/50
TCA	0	50	50/0	50/0	50/0
	250	50	50/0	50/0	50/0
	500	50	50/0	50/0	50/0
	750	50	50/0	50/0	50/0
	1000	50	5/45	6/44	5/45
	1250	50	0/50	0/50	0/50
	1500	50	0/50	0/50	0/50
	1750	50	0/50	0/50	0/50
	2000	50	0/50	0/50	0/50
OXY	0	50	50/0	50/0	50/0
	25	50	50/0	50/0	50/0
	50	50	50/0	50/0	50/0
	75	50	50/0	50/0	50/0
	100	50	6/44	6/44	5/45
	125	50	0/50	0/50	0/50
	150	50	0/50	0/50	0/50
	175	50	0/50	0/50	0/50
	200	50	0/50	0/50	0/50
BUP	0	50	50/0	50/0	50/0
	2.5	50	50/0	50/0	50/0
	5.0	50	50/0	50/0	50/0
	7.5	50	50/0	50/0	50/0
	10.0	50	6/44	4/46	4/46
	12.5	50	0/50	0/50	0/50
	15.0	50	0/50	0/50	0/50
	17.5	50	0/50	0/50	0/50
	20.0	50	0/50	0/50	0/50

Specificity and cross reactivity

To test the specificity of the test, the test device was used to test various drugs, drug metabolites and other components of the same class that are likely to be present in urine. All the components were added to drug-free normal human urine. The following structurally related compounds produced positive results with the test when tested at levels equal to or greater than the concentrations listed below.

Item	Concentration (ng/mL)	Item	Concentration (ng/mL)
Amphetamine (AMP)		**Methamphetamine (MET)**	
d-Amphetamine	1,000	D(+)-Methamphetamine	1,000
d,l-Amphetamine	3,000	D-Amphetamine	50,000
1-Amphetamine	50,000	Chloroquine	50,000
(+/-) 3,4-methylenedioxyamphetamine (MDA)	5,000	(+/-)-Ephedrine	50,000
Phentermine	3,000	(-)-Methamphetamine	25,000
d-methamphetamine	>100,000	(+/-)3,4-methylenedioxumethamphetamine(MDMA)	2,000
l-methamphetamine	>100,000	β-Phenylethylamine	50,000
3,4-Methylenedioxyethylamphetamine(MDE)	100,000	Trimethobenzamide	10,000
(+/-)3,4-methylenedioxumethamphetamine	100,000	**Methylenedioxymethamphetamine (MDMA)**	
Barbiturates (BAR)		3,4-Methylenedioxymethamphetamine HCl (MDMA)	500
Secobarbital	300	3,4-Methylenedioxyamphetamine HCl (MDA)	3,000
Amobarbital	300	3,4-Methylenedioxyethylamphetamine (MDE)	300
Alphenol	150	**Morphine (MOP/OPI300)**	
Aprobarbital	200	Morphine	300
Butabarbital	75	Codeine	300
Butathal	100	Ethyl Morphine	300
Butalbital	2,500	Hydrocodone	5,000
Cyclopentobarbital	600	Hydromorphone	5,000
Pentobarbital	300	Morphine-3-β-d-glucuronide	1,000
Phenobarbital	10,000	Thebaine	30,000
Benzodiazepines (BZO)		**Opiate (OPI2000)**	
Oxazepam	300	Morphine	2,000
Alprazolam	200	Codeine	2,000
a-Hydroxyalprazolam	1,500	Ethylmorphine	5,000
Bromazepam	1,500	Hydrocodone	12,500
Chlordiazepoxide	1,500	Hydromorphine	5,000
Clonazepam HCl	800	Levorphanol	75,000
Clobazam	100	6-Monoacetylmorphine	5,000
Clonazepam	800	Morphine 3-β-D-glucuronide	2,000
Clorazepate dipotassium	200	Norcodeine	12,500
Delorazepam	1,500	Normorphone	50,000
Desalkylflurazepam	400	Oxycodone	25,000
Diazepam	200	Oxymorphine	25,000
Estazolam	2,500	Procaine	150,000
Flunitrazepam	400	Thebaine	100,000
D,L-Lorazepam	1,500	**Phencyclidine (PCP)**	
Midazolam	12,500	Phencyclidine	25
Nitrazepam	100	4-hydroxyphencyclidine	12500
Norchlordiazepoxide	200	**Tri-cyclic Antidepressants (TCA)**	
Nordiazepam	400	Nortriptyline	1,000
Temazepam	100	Nordoxepin	1,000
Triazolam	2,500	Trimipramine	3,000
Marijuana (THC)		Amitriptyline	1,500
11-nor-Δ9-THC-9-COOH	50	Promazine	1,500
11-nor-Δ8-THC-9-COOH	30	Desipramine	200
11-hydroxy-Δ9-Tetrahydrocannabinol	2,500	Imipramine	400
Δ8- Tetrahydrocannabinol	7,500	Clomipramine	12,500
Δ9- Tetrahydrocannabinol	10,000	Doxepin	2,000
Cannabinol	100,000	Maprotiline	2,000
Cannabidiol	100,000	Promethazine	25,000
Cocaine (COC)		**Oxycodone(OXY)**	
Benzoylecgonine	300	Oxycodone	100
Cocaine HCl	750	Dihydrocodeine	20,000
Cocaethylene	12,500	Codeine	100,000
Ecgonine	32,000	Hydromorphone	100,000
Methadone (MTD)		Morphine	>100,000
Methadone	300	Acetylmorphine	>100,000
Doxylamine	50,000	Buprenorphine	>100,000
Buprenorphine(BUP)		Ethylmorphine	>100,000
Buprenorphine	10		
Buprenorphine -3-D-Glucuronide	15		
Norbuprenorphine	20		
Norbuprenorphine 3-D-Glucuronide	200		

Adulteration/Specimen Validity Test

Cr: Creatinine reacts with a creatinine indicator in an alkaline medium to form a purplish-brown color complex if creatinine in the urine is present at the normal level. The color intensity is directly proportional to the concentration of creatinine. A urine sample with creatinine concentration of less than 20 mg/dL produces a very light, or no pad color change, which indicates adulteration in the from of specimen dilution.

S.G.: The specific gravity test is based on the pKa change of certain pretreated polyelectrolytes in relation to the ionic concentration. The pad colors will change from dark blue to blue-green in urine of low ionic concentration to green and yellow-green in urine of higher ionic concentration. A urine specific gravity below 1.005 or above 1.025 is considered abnormal.

OX: Bleach or other oxidizing agents react with an oxidant indicator to form a color complex. Observation of a blue-green, medium to dark brown, or orange color indicates adulteration with bleach or other oxidizing agents.

pH: Normal urine pH ranges from 4.5 to 8.0. Values below pH 4.0 or above pH 9.0 are indicative of adulteration.

Gl.: Glutaraldehyde is not a natural component of human urine and it should not be present in normal urine. The presence of glutaraldehyde in the urine sample indicates the possibility of adulteration. However, false positive may result when ketone bodies are presence in urine. Ketone bodies may appear in urine when a person is in ketoacidosis, starvation or other metabolic abnormalities.

NI.: Although nitrite is not a normal component of urine, nitrite levels of up to 3.6 mg/dl may be found in some urine specimens due to urinary tract infections, bacterial contamination or improper storage. In this adulteration control, nitrite level above 7.5 mg/dl is considered abnormal.

Pyridium Chlorochromate: The presence of any chromate in urine is indicative of adulteration as chromate is not a normal constituent of urine.

Interfering substances

Clinical urine samples may contain substances that could potentially interfere with the test. The following compounds were added to drug-free urine, with a drug concentration 25% below the cutoff, and urine with a drug concentration 25% above the cutoff and were tested with the UScreen drugs of abuse test. All potential interferents were added at a concentration of 100 µg/mL. None of the urine samples showed any deviation from the expected results.

Acetominophen (4-Acetamidophenol) **(except OXY test)**
Acetophenetidin
N-Acetylprocainamide **(except OXY test)**
Acetylsalicylic acid
Aminopyrine
Amoxicillin
Ampicillin
Apomorphine
Aspartame
Atroine **excet BAR test**
Benzilic acid
Benzoic acid
Benzoylecgonine **(except COC,OXY test)**
Bilirubin
Cannabidiol **(except THC, OXY tests)**
Chloralhydrate
Chloramphenicol
Chlorothiazide
Chlorpromazine
Chlorquine
Cholesterol
Clonidine
Codeine **(except MOP/OPI300, BZO, OXY tests)**
Cortisone
(-) Cotinine
Creatinine
Deoxycorticosterone
Dextromethorphan
Diclofenac
Diflunisal
Digoxin
Diphenhydramine
Ecgonine methyl ester
Erythromycin **(except BZO test)**
β-Estradiol **(except BZO test)**

Fenoprofen
Furosemide
Gentisic acid
Hydralazine **(except BZO test)**
Hydrochlorothiazide **(except BZO test)**
Hydrocodone **(exceptBZO, MOP/OPI300,OXY test)**
Hydrocortisone
O-Hydroxyhippuric acid
3-Hydroxytyramine
Ibuprofen **(except OXY test)**
D,L-Isoproterenol **(except AMP, BAR test)**
Isoxsuprine
Ketamine **(except OXY test)**
Ketoprofen
Labetalol
Loperamide
Maprotiline **(except TCA, OXY tests)**
Meperidine **(except THC, OXY tests)**
Meprobamate
Methadone **(except MTD, OXY tests)**
Methoxyphenamine **(except AMP,BAR test)**
Morphine-3-β-d-glucuronide **(except BZO, MOP/OPI300 tests)**
Nalidixic acid
Naloxone
Naltrexone
Naproxen
Niacinamide
Nifedipine
Norcodein **(except MOP/OPI300, BZO, OXY tests)**
Norethindrone
D-Norpropoxyphene
Noscapine
D,L-Octopamine
Oxalic acid
Oxazepam **(except BZO, OXY tests)**

Oxolinic acid
Oxymetazoline
Papaverine
Penicillin-G
Pentobarbital **(except BZR, OXY test)**
Perphenazine
Phenelzine
Phencyclidine **(except PCP, OXY tests)**
Prednisone
Procaine **(except BZO, MOP/OPI300, OXY tests)**
DL-Propranolol
D-Propoxyphene **(except OXY, test)**
D-Pseudoephedrine **(except AMP, BAR tests)**
Quinine
Ranitidine
Salicylic acid
Secobarbital **(except BAR, OXY tests)**
Serotonin (5- Hydroxytyramine)
Sulfamethazine
Sulindac
Tetrahydrocortisone, 3-acetate **(except AMP, BAR, OXY tests)**
Tetrahydrocortisone 3-(β-Dglucuronide) **(except AMP, BAR, OXY tests)**
Tetrahydrozoline
Thiamine
Thioridazine
Triamterene
DL-Tyrosine
Trifluoperazine
Trimethoprim
D L-Tryptophan **(except AMP, BAR tests)**
Tyramine **(except AMP, BAR tests)**
Uric acid
Verapamil
Zoloft
Zomepirac

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INDEX OF SYMBOLS

Keep away from sunlight
Store between 39°F-86°F (4°C-30°C)
Keep dry
Do not re-use

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