PROTOCOL

TITLE: Ketamine Assisted Psychotherapy for Opioid Use Disorder

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SPONSOR ORGANIZATION:	**UNIVERSITY OF UTAH**
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Summary of Changes from Protocol Version 1.0 to Version 2.0

In addition to corrections to typographical errors and spelling mistakes, the following changes were made to convert version 1.0 to version 2.0:

1. Before the study was registered on clinicaltrials.gov and before recruitment or enrollment began, the primary outcome was changed from time to opioid lapse to total number of instances of illicit drug use measured by the Timeline Followback Procedure. This change in primary outcome was informed by pilot study results in people receiving medications for OUD indicating that MORE significantly reduced instances of drug use as measured by the TLFB (Cooperman et al., 2021, *Journal of Substance Abuse Treatment*). Given that MORE seemed to positively impact the total number of instances of drug use (across all drugs of abuse) as measured as a continuous outcome, we changed the primary outcome measure before registering the trial and before enrolling the first study participant. Our primary outcome analysis approach was also changed accordingly from a survival analysis of time to opioid lapse to a generalized linear mixed model of instances of illicit drug use.

2. In the original protocol we only included patients in early recovery (>1 but <6 months of buprenorphine use) but in 2021 expanded inclusion criteria to include patients with >6 months of buprenorphine use.

3. The Metacognitive Processes of Decentering (MPODS) scale was added as an assessment of mindfulness-related processes.

4. A visual analogue scale (VAS) was added as an assessment of opioid craving, in addition to the Desires for Drug Questionnaire.

CONTENTS

1. INTRODUCTION

This document is a protocol for a human research study to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations, and institutional research policies and procedures.

2. STUDY OBJECTIVES

The purpose of this study is to conduct a Stage 1 randomized controlled trial to test a potential optimization of the evidence-based Mindfulness-Oriented Recovery Enhancement (MORE) intervention for opioid use disorder (OUD). Here we will add Ketamine to MORE (MORE+KAP) and test the MORE+KAP intervention versus the standard MORE intervention in a sample of patients undergoing medication assisted treatment (MAT) who are receiving suboxone for OUD.

The Specific Aims of this study are as follows:

AIM 1. To assess the safety of Mindfulness-Oriented Recovery Enhancement (MORE) + ketamine assisted psychotherapy (KAP) for patients with OUD treated with buprenorphine.

AIM 2. To test the preliminary efficacy of Mindfulness-Oriented Recovery Enhancement (MORE) + ketamine assisted psychotherapy (KAP) for patients with OUD treated with buprenorphine.
Hypotheses: MORE+KAP will be associated with significantly greater improvements in addiction-related outcomes than MORE alone.

3. BACKGROUND

Opioid use disorder (OUD) remains one of our nation's greatest public health burdens, affecting 2.1 million US citizens (Azadfard, Huecker, & Leaming, 2019). In 2017, the US saw nearly 50,000 opioid overdose deaths and declared opioid overdose a national emergency (CDC, 2020). Core symptoms of OUD include an inability to self-regulate craving, repeated administration despite consequential physical or psychological harm, and hypervigilance to drug-related cues caused by dysregulation of the reward system. These symptoms further exacerbate the downward spiral of addiction.

Research has demonstrated that medication-assisted treatment (MAT) is currently the most effective treatment for individuals with OUD. One of the most common medications used for OUD is suboxone, a combination of buprenorphine and naltrexone. Suboxone has demonstrated efficacy for reducing overdose, craving, and mortality rate (Schwartz et al., 2013). Nonetheless, approximately half of patients treated with Suboxone relapse within six months, suggesting that additional adjunctive interventions are needed to improve outcomes.

Many questions still remain unanswered regarding disparities in MAT, such as efficacy for individuals across the spectrum of opioid use and severity, combination therapy with behavior and/or other pharmacological approaches, optimal duration of treatment, and comorbidity. Previous research has shown that mindfulness-based interventions (MBI) can be used to treat substance use disorders by reducing craving and dependence while improving mental health and well-being (Sancho et al., 2018). Mindfulness is a type of psychological training that involves an awareness of one's experiences of the present moment in a non-judgemental way. A new and novel multimodal mindfulness-based intervention called Mindfulness-Oriented Recovery Enhancement (MORE) is unique compared to other MBIs in that it combines traditional mindfulness exercises with incorporating savoring and reappraisal techniques that are specifically designed to target and remediate dysfunction in corticostriatal neural reward circuitry that subserves and maintains addiction. Dysfunction in this circuit is maintained by aberrant glutamatergic signalling, whereby drug cues elicit release of excess glutamate, causing hyperactivation between the orbitofrontal cortex and the striatum and propelling drug craving and compulsive drug use (Kalivas & Volkow, 2005). MORE has been shown to modulate activity in these brain regions during the processing of drug and natural rewards (Froeliger et al., 2017). The effects of MORE on reducing opioid misuse are mediated by the restructuring of neural reward processing (Garland et al., 2019).

While suboxone is a standard MAT treatment for OUD at UNI, both MORE and KAP are investigational therapies.

MORE has demonstrated efficacy for reducing opioid misuse and OUD in five RCTs In a NIDA-funded (R03DA032517) Stage 2 RCT (N=115), MORE significantly decreased the proportion of patients meeting criteria for OUD (reduced OUD by 63%; $\chi 2=3.74$, $p \leq .05$), and reduced opioid craving ($p=.027$, $d=.50$), and pain severity ($p=.014$, $d=.63$) relative to a supportive group psychotherapy (SG) control condition (Garland et al. 2014). Additionally, MORE decreased opioid cue-reactivity relative to the SG, and significantly increased HRV responses that were associated with reduced opioid craving and misuse (Garland et al., 2014, 2017). A second Stage 2 RCT (N=95) conducted in a primary care setting replicated these results, demonstrating that MORE significantly decreased opioid misuse ($p=.027$, $d=.64$) and pain severity ($p=.03$, $d=.54$) (Garland et al., 2019). In secondary outcomes from this trial, MORE significantly reduced opioid dose by 3-month follow-up ($p=.006$, $d=1.07$) – a 32% reduction in morphine milligram equivalents (MME) (Garland et al., 2020). In a third NIH-funded Stage 1 RCT of patients with OUD and pain (N=30), we found using ecological momentary assessment (EMA) that MORE reduced opioid craving by 50% (Garland et al, 2019). Also, relative to usual MOUD treatment, MORE was associated with fewer days of heroin use, fewer days of other illicit drug use, and less psychiatric distress. In a SAMHSA-funded Stage 3 RCT (N=180) including patients with OUD, MORE significantly reduced craving and PTSD symptoms relative to CBT and treatment-as-usual (Garland et al., 2016). Finally, we recently completed post-treatment data collection for PI Garland's current NIDA R01-funded full-scale efficacy test (N=250), and found MORE significantly decreased opioid misuse ($p=.028$, $d=.37$), as triangulated by an objective Drug Misuse Index (DMI) of blinded clinician ratings and urine toxicology ($p=.01$ – a 45% reduction in occurrence of misuse by 9 months) Taken together, data across these 5 RCTs conducted

by MPI Garland indicate that MORE is an efficacious treatment for improving clinical outcomes among opioid users.

Despite the successes of the MORE treatment approach, approximately half of patients do not show an adequate treatment response. Combining MORE with novel pharmacologic agents may increase its efficacy as a treatment for OUD. Given that glutamatergic dysregulation is essential to the neural dysfunctions undergirding addictive behavior, it stands to reason that a glutamatergic agent might boost the efficacy of MORE. Ketamine, a FDA-approved medication that is one of the most commonly used anesthetic agents in the world, has glutamate antagonist properties that has already demonstrated efficacy for the treatment of depression and has shown promise for the treatment of other psychiatric disorders - including addiction.

Subanesthetic doses of ketamine have recently been FDA approved in the U.S. as a treatment for depression. Due to its rapid-acting effects, minimal adverse events, relatively low cost, and exceptional therapeutic index, ketamine is seen as a promising treatment for many mental health disorders (Craven, 2007). It has been hypothesized that glutamatergic dysregulation in the PFC and mesolimbic regions of the brain may play a role in the neuropathology of substance use disorder (Marquez et al., 2017). The pharmacological mechanism that ketamine utilizes is generally attributed to NMDA receptor antagonism, which inhibits glutamate transmission.

Given its promising pharmacologic properties and its positive safety profile, researchers have begun to explore the combination of subanesthetic doses of ketamine and psychotherapy - known as Ketamine Assisted Psychotherapy (KAP). For instance, a clinical trial of KAP for alcohol and OUD and found that subanesthetic doses of ketamine produced complete abstinence for more than one year in 66% of patients as compared to just 24% in the placebo-controlled group (Krupitsky & Grinenko, 1997). More recently, a team from Columbia University conducted a RCT of KAP for cocaine use disorder using IV doses of 0.5 mg/kg, and found that KAP significantly improved abstinence rates and prevented relapse (Dakwar et al., 2019). The therapeutic effects of KAP have been shown to be mediated by changes in self-awareness and self-referential processing (Dakwar et al., 2019). Given that aberrant self-referential processing encoded in the default mode networks has been shown to be linked with greater addiction severity (Wilcox et al., 2019), using KAP to modulate self-referential processing may potentiate MORE and improve OUD treatment outcomes.

Here we propose that a combination of subanesthetic doses of ketamine in conjunction with a structured therapeutic process and MORE may provide a superior treatment for patients with OUD via glutamatergic mechanisms and associated changes in self-referential processing.

4. STUDY DESIGN

This study is a parallel groups randomized controlled trial. Outcomes are assessed at baseline, after the 8-week study treatments, and at 3-month follow-up (study month 5).

4.1 Number of Subjects

This study is powered based on previous trials evaluating ketamine assisted psychotherapy for cocaine and alcohol use disorder. The Dakwar et al. (2019) trial had a N=55, and found a large effect size for ketamine treatment of cocaine use. Based on our power analysis, N=54 will provide power >0.80 to estimate large effects on drug use. However, patients with OUD often have unstable lives that make research participation Thus, we will aim to randomize 68 participants by to account for a 20% attrition rate.

4.2 Subject Selection and Withdrawal

4.2.1 Inclusion and Exclusion Criteria

Table 1 lists the inclusion and exclusion criteria for screening patients for participation in the trial.

Table 1: Inclusion and Exclusion Criteria
Inclusion Criteria • Age 18+ • Diagnosis of opioid use disorder • Receiving OUD treatment with a buprenorphine treatment
Exclusion Criteria • Previous experience with a mindfulness-based intervention program • Pregnancy • Any serious medical, mental, or cognitive issue that prevents successful participation in a mindfulness-based group treatment program • Prior use of ketamine other than as prescribed by a physician • Any of the following medical conditions: Blood Vessel Disease Heart Valve Disease Heart Failure Class 2 or Above Heart Disease Pregnancy/Breastfeeding Arteriovenous Malformation History of Intracranial Bleeding or Stroke History of Seizures Hypoxia defined by current need for supplemental oxygen Liver Disease History of allergic reaction to Ketamine Dementia (moderate-severe) History of Psychotic Disorder, Bipolar Disorder, or Personality Disorder Dissociative Identity Disorder

Because participants must be able to receive the MORE treatment in English, it is not feasible to enroll participants who do not speak English.

4.3 Screening, Recruitment, and Enrollment

4.3.1 Screening

Patients aged 18 or older will be identified via the University of Utah Health system electronic health record (EHR) andsubsequently screened. Patients will also be referred by their health care practitioner into the study, or notified about the study via print and online advertisements. Screening will occur in clinic, over the phone, or in person at the Center on Mindfulness and Integrative Health Intervention Development (C-MIIND).

Screening questions assess OUD diagnosis and duration of treatment with buprenorphine-containing products.

4.3.2 Recruitment and Enrollment

Patients who screen positive will be informed about the study during an interview, during which the recruiter will confirm the absence of any exclusion criteria, review the purpose of the study, answer any questions and, after obtaining written informed consent, collect baseline data on: key demographic characteristics, clinical characteristics, and primary, secondary, and mechanistic outcomes. Recruitment staff will be kept blinded to randomization status of the patients and will be rigorously trained to reduce potential bias.

4.3.3 Early Withdrawal of Participants

Because this trial is conducted via the "intent-to-treat" (ITT) framework, all participants will be analyzed in the group to which they were randomly assigned, regardless of whether they complete the intervention or are noncompliant. This preserves the effect of randomization. We plan to follow participants for the study outcomes even if they elect to stop the study intervention. If the participant elects full withdrawal from the study, this will be recorded and all contact with the participant will cease. Participants who are disruptive, or who develop active suicidality or psychosis, or medical conditions that would preclude completion of study procedures, may be withdrawn at any time by the discretion of the PI.

5. EXPERIMENTAL INTERVENTION

The **MORE + KAP arm** will participate in 8 weekly, 2-hour group sessions led by a Master's level clinical social worker. MORE sessions involve mindfulness training to disrupt addictive behavior and craving, cognitive reappraisal to decrease negative affect, and savoring to augment natural reward processing and amplify positive emotion. MORE participants will be asked to engage in 15 minutes/day of skill practice at home, and complete daily EMA.

For the **MORE+KAP** groups, MORE will be adapted as a behavioral platform for psychedelic-assisted psychotherapy. In MORE session 5, in addition to introducing a mindfulness of craving technique, psychedelic preparation material will be delivered, including education about ketamine effects and mindfulness techniques to address anxiety and uncomfortable ketamine symptoms. The next week, participants will receive a KAP session with IM ketamine at 0.5 mg/kg. They will then return for MORE session 6 which will be focused on psychedelic integration procedures to explore the phenomenology and meaning of the ketamine experience, with a focus on how mindfulness can facilitate mystical, self-transcendent experiences occasioned by ketamine and how such experiences may promote addiction recovery. Later that week participants will receive another KAP session with IM ketamine at 1.0 mg/kg. Following the second KAP session, there will be two MORE sessions (sessions 7 & 8) focused on psychedelic integration and relapse prevention.

KAP. Ketamine hydrochloride (0.5 mg/kg in dosing session 1, up to 1.0 mg/kg in dosing session 2 unless not well-tolerated, in which case the dose will be increased to 0.75 mg/kg or kept at 0.5 mg/kg). Blood pressure, heart rate, respiration, and oxygen saturation will be monitored for two hours post-ketamine administration. Medical monitoring and psychological support will be provided by a psychiatrist during and up to two hours after IM dosing. Ketamine has been shown to enhance addiction memory retrieval and extinction to reduce substance use. We will mirror this retrieval-extinction process beginning the session by asking the patient to retrieve and discuss their OUD memories and history of drug use. IM ketamine will then be administered with a syringe (a potential cue for memory retrieval for patients with IV drug use), and then 1 hour later participants will be guided in a mindfulness technique to facilitate extinction of addiction-related memories arising during the KAP session.

6. CONTROL INTERVENTION

The **MORE-only arm** will participate in 8 weekly, 2-hour group sessions led by a Master's level clinical social worker. MORE sessions involve mindfulness training to disrupt addictive behavior and craving, cognitive reappraisal to decrease negative affect, and savoring to augment natural reward processing and amplify positive emotion. MORE participants will be asked to engage in 15 minutes/day of skill practice at home, and complete daily EMA.

7. OUTCOME MEASURES

7.1 Definition and Ascertainment of Outcomes

7.1.1. *Primary outcomes (PRE/POST/FOLLOW-UP).* Given the high rate of polysubstance use among people with OUD, our prespecified primary outcome is the number of instances of illicit drug use in the past 30 days, summed across all drug types used (i.e., opioids, cocaine/crack, amphetamines, marijuana, hallucinogens,

inhalants, benzodiazepines, but not including prescribed cannabis or other prescribed medications), as assessed with the validated Timeline Followback method.

7.1.2. *Secondary outcomes (PRE/POST/FOLLOW-UP* Secondary outcomes include days of buprenorphine use measured by the Timeline Followback, opioid craving measured with a 0-100mm visual analogue scale (VAS) and the Desires for Drug Questionnaire (DDQ); and the Depression Anxiety Stress Scale (DASS). Mindfulness-related processes will be assessed with the Metacognitive Processes of Decentering Scale. The Nondual Awareness Dimensional Assessment (NADA) will assess self-transcendence.

7.1.3. *Other outcomes (PRE/POST).*
State mindfulness will be assessed with the Toronto Mindfulness Scale (TMS) in a laboratory-based mindfulness meditation task. All participants will receive the same instruction: “Now practice mindfulness, which means focusing on your thoughts, feelings and body sensations in the present moment in a nonjudgmental way, without reacting to them.” In keeping with methods used in previous mindfulness studies, to control for demand characteristics, these task instructions were kept constant across both treatment arms, allowing us to isolate the effects of treatment from any potential instruction effects. Interoceptive awareness will be assessed with the Multidimensional Assessment of Interoceptive Awareness (MAIA). Mystical and self-transcendent experiences during ketamine administration will be assessed with the MEQ and the NADA-State version. Reappraisal will be assessed with the Emotion Regulation Questionnaire (ERQ) and savoring will be assessed with the Brief Savoring Inventory. Meaning in life will be assessed with the Meaning in Life questionnaire (MLQ). Ecological momentary assessments (EMA) via smartphone will be used to collect craving, affective symptoms, and drug use (however, because EMA compliance is likely to be low in this population, the Timeline Followback is the primary outcome measure used to assess drug use).

8. STUDY PROCEDURES AND VISITS

8.1 Randomization

The trial has a two-group parallel randomized design. The unit of randomization is the individual patient. Following pre-intervention assessment, patients will be assigned in a 1:1 ratio to undergo MORE+KAP or MORE alone.

9. STATISTICAL ANALYSIS, SAMPLE SIZE AND POWER CALCULATIONS

9.1 Design Overview

This is a two-group, parallel randomized controlled superiority trial.

9.2 Subject Allocation to Treatment Arms

An electronic random number generator will randomize participants with simple random assignment in blocks of varying sizes (2 - 4) to preserve unpredictability of allocation. To prevent bias and maintain allocation concealment, participants will not be allocated until the first treatment session. To maintain blinding, the allocation list was inaccessible to project staff involved in assessment or treatment, and before each assessment, participants were reminded to not reveal anything that would disclose their treatment assignment to study staff.

9.3 Sample Size

This study is powered based on previous trials evaluating ketamine assisted psychotherapy for cocaine and alcohol use disorder. The Dakwar et al. (2019) trial had a N=55, and found a large effect size for ketamine treatment of cocaine use. Based on our power analysis, N=54 will provide power >0.80 to estimate large effects on drug use. However, patients with OUD often have unstable lives that make research participation difficult – resulting in a high dropout rate even before random allocation and study treatments have occurred. Thus, we will aim to randomize 68 participants by to account for a 20% attrition rate.

9.4 Interim Monitoring

Interim monitoring will focus on safety, patient accrual, baseline comparability of treatment groups, protocol adherence, data completeness and quality, and safety. No interim outcome analysis is planned. Thus, we propose that early termination of the project will occur only when the safety analysis of the project indicates as such. This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) any new information becomes available during the trial that necessitates stopping the trial; or (3) other situations occur that might warrant stopping the trial**.**

9.5 Statistical Analysis Plan

9.5.1. We will inspect scatter plots and descriptive statistics for study variables at pre-treatment, post-treatment, and the follow-up to determine the pattern of performance across time. After data cleaning, we will examine the empirical distribution function of all variables.

9.5.2. To assess primary drug use outcomes, we will use generalized linear mixed models (GLMMs) with a constrained longitudinal approach, equating pre-treatment drug use means across treatment arms. Treatment effect will be specified as a fixed effect and models will include a random intercept. Because the data represent instances of drug use, Poisson distribution will be specified to accommodate non-normal count data. Analyses will include both complete case data and multiple imputation to address missing values. For sensitivity analyses, we will use a GLMM with multiple imputation, adjusting for potential confounders including number of DSM-5 opioid use disorder (OUD) symptoms (i.e., OUD severity), and MOUD treatment characteristics (i.e., duration and dosage of buprenorphine treatment). Other confounders will be considered for inclusion as covariates if they meet a $p<0.10$ significance level. We will also conduct a per-protocol sensitivity analysis focused on patients who adhered to their assigned treatment. Poisson regression models, with and without zero-inflation (necessary in the case that there are many participants who remain abstinent during the trial), will estimate the effect of MORE+KAP on drug use at post-treatment and follow-up.

To assess secondary outcomes, linear mixed models (LMMs) will be computed with multiple imputation (10 iterations), with a constrained longitudinal approach, equating pre-treatment drug use means across treatment arms. Changes in state mindfulness following the mindfulness meditation task will be analyzed with LMM.

10. DATA MANAGEMENT

Data will be collected from the participants for research purposes only. Data will be collected from the subjects at pre and post-intervention, as well as at the 3-month post-intervention follow-up (study month 5). Materials will be stored in the locked office of the PI prior to and during processing. Data management will include entry of pre-, post- and follow-up data directly into a designated computer (see Resources) for processing, with double entry to verify the accuracy of data. All computer data will be password protected and maintained on a computer in the PI's locked office, and participant information will be identified only by study identification numbers. Participants will be asked to provide contact information for follow-up purposes only. For added security, participant contact information will be removed from the original database and stored in a separate location. A separate record linking participant names and contact information to participant ID numbers will be created and stored separately in a password protected file. Only project staff will have access to subject identities. All necessary steps will be taken to ensure subject confidentiality.

10.1.1. *Research Materials Handling*: All materials derived from the study will be handled only by study personnel during collection, storage, and in subsequent data analysis. The PI is experienced in conducting clinical studies and is fully aware of the need for anonymity, privacy and security, and maintains strict surveillance of the office environment. No incidents of violation of patient confidentiality have occurred in the previous studies in which the PI has participated.

10.1.2. *Handling of Study Treatment Recordings*. We will use a password protected, secure file transfer protocol to maintain security of study treatment recordings when they are sent to fidelity monitors.

10.1.3. Data Monitoring Procedures: There will be weekly meetings of the research team led by the PI for monitoring progress, reviewing recruitment goals, evaluation of lapsed participation, and review of missing data. Plans for remediation of missing information and lapsed participation will be formulated by the PI at those times as needed.

10.1.4. Data Risk Reporting: The Study Coordinator will be responsible for compiling recruitment numbers, completing assessments, maintaining databases, and identifying missing data and lapsed participation. They will report this information to the PI at weekly meetings.

10.1.5. Data Integrity: Data integrity will be monitored closely. All personnel will have undergone Good Clinical Practice (GCP) training prior to study initiation and will be human subjects/ethics certified. Study records will be entered into the password protected, secure study database (backed up on a secure server).

11. SAFETY AND ADVERSE EVENTS

11.1 Background

This section describes the requirements and processes for reporting adverse events (AE), serious AE (SAE) and unanticipated problems to the IRB.

11.2 Definitions

Adverse Event: Because 45 CFR 46 does not provide a specific definition for an adverse event (AE), the definition of an AE will conform to the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. The same definition is used by the U.S. Food and Drug Administration (FDA) except that "drug" is typically used instead of the term "intervention." An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered an intervention and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational intervention, whether or not related to the intervention.

Serious Adverse Event (SAE): Any AE that:

- Results in death;
- Is life threatening, or places the participant at immediate risk of death from the event as it occurred;
- Requires or prolongs hospitalization;
- Causes persistent or significant disability or incapacity;
- Results in congenital anomalies or birth defects;
- Is another condition, which the investigators judge to represent significant hazards.

Unanticipated Problem: any incident, experience, or outcome that meets all of the following criteria:

- 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 study population;
- Related or possibly related to participation in the research; in this guidance document, 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;
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Adverse Event Reporting Period: The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up.

Preexisting Condition: A preexisting condition is one that is present at the time of providing the consent for the study. A preexisting condition is considered an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

11.3 Ascertainment of AE, Unanticipated Problems (UP), and SAE

Study staff will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

Unanticipated problems will be recorded in the data collection system throughout the study.

During the performance of the study, the participants will be monitored by research personnel associated with the project (coordinator, research assistant) or the investigators themselves. All the volunteers will have direct access to the phone numbers of the study coordinator and the responsible clinician, as well as an additional 24-hour contact number (emergency room services). These numbers are additionally included in the consent form provided to the volunteers. They will be informed of all the possible adverse events that could be encountered during the study. They will be encouraged to contact the investigators if they notice any adverse events. The investigators have ample prior experience in the utilization of the protocols utilized in the studies.

Although a life-threatening event or long-term life-compromising effect due to the study treatments is unlikely, we will implement several monitoring approaches to ensure patient safety. One is a “top-down” approach, in which after a “medically/psychologically serious event” occurs, we will investigate whether the event is indeed an adverse effect due to our protocol. We also will assess ketamine-related AEs (i.e., side effects) systematically after each ketamine dosing session. The other is a “bottom-up” approach. All participants will be asked to report adverse events to the therapists, the study clinician, and the study coordinator. Participants will also be strongly encouraged to discuss with the research staff anything they feel to be an adverse event or other issues that are problematic for them about the study. Adverse events will be recorded and reported to the PI, co-investigators, and the University of Utah IRB.

In the event of a report of a possible adverse event, the participant will be seen as soon as possible by the PI, the study clinician, or Clinical Research Coordinator for an evaluation. The level of care will be determined and the participant referred appropriately for care, which may involve the resources of the University Primary Care Clinics, the University of Utah Hospital, or the University Neuropsychiatric Institute. The study clinician will not provide medical care directly but will provide advice with regard to the appropriate type of medical care, and helping the participant obtain that level of care. If the PIs, treating physician, or the participant believes that a serious adverse event resulting from the study has occurred, the PI will immediately notify the University of Utah IRB. Further involvement in the study by that participant may be terminated.

Hence, several mechanisms will be in place to identify participants who may be experiencing adverse effects during the study: 1) communication between participants and the research staff; 2) direct, weekly observation of participant’s health status by the therapists and during physician monitoring at the follow-up sessions; and 3) verbal inquiry concerning potential adverse affects through weekly review by the therapists.

11.4 Reporting of Unanticipated Problems and Serious Adverse Events

A summary report of the UP and SAE collected by all methods of ascertainment will be prepared for the Data Safety and Monitoring Committee and IRB in accordance with the Safety Monitoring Plan.

5. ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Good Clinical Practice Statement

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration

of Helsinki, and that are consistent with the ICH guidelines for Good Clinical Practice (GCP) and all federal as well as local regulatory requirements.

12.2 Informed Consent

The principles of informed consent are described in ICH guidelines for GCP (ICH E6[R1]).

As noted previously in the screening procedures outlined above, participants identified by EHR data pull will be contacted by phone if they do not otherwise opt out. Following phone screening, informed written consent will be obtained by trained study personnel with all potential participants receiving a general description of the study, including the study specific baseline evaluations, along with the study specific evaluations.

12.3 Institutional Review Board

The University of Utah IRB will be responsible for review and approval of the protocol, any amendments, the informed consent form (ICF) and any other materials provided to participants. The IRB will be informed of any event likely to affect the safety of the participant or the continued conduct of the trial. Records of IRB review and approval of study protocol, ICF, and amendments will be kept by the PI.

12.4 Risks to Human Subjects

The main study procedures include a clinical evaluation, completion of questionnaires, drug screens, involvement with a behavioral intervention, and administration of ketamine-assisted psychotherapy (KAP).

Risks associated with IM ketamine administration include transient elevation in heart rate and blood pressure, transient visual changes including blurry vision, dizziness, impaired coordination, anxiety or paranoia, nausea, and headache as well as injection site irritation. Acute ketamine effects can involve dissociation, disorientation, confusion, visual and other sensory changes, alterations to sense of time. Ketamine when abused at high and frequent doses has been demonstrated to cause inflammatory changes in the lower urinary tract, termed ketamine-induced cystitis—however this has not been demonstrated a significant concern when ketamine is used in clinical settings. Ketamine has demonstrated abuse potential and is known as a recreational drug of abuse. However with doses and frequency used in clinical settings there is minimal risk of abuse potential or kindling. We will closely monitor for adverse events including increased drug use, emergence of new substance use, ketamine misuse, and psychiatric disturbances. Because of ketamine acute effects study participants will be required to have transportation home from the treatment session and are required to not operate a motor vehicle or engage in vigorous physical activity for at least 8 hours following treatment.

Risks associated with MORE are minimal. There is *no evidence* that MORE activities worsen symptoms of OUD. In the PI's prior R01-funded trials of MORE, no adverse events related to participation in MORE were reported by participants. Anecdotal reports and small observational studies suggest that participation in mindfulness meditation may increase anxiety or distress in some patients. That said, in multiple RCTs we demonstrated that MORE reliably decreases symptoms psychological distress. Since anxiety is a known aggravator of OUD relapse, participants will be advised to inform their MORE providers of any significant shift in their symptoms for the worse while taking part in the MORE intervention. Reports of such changes will be given to the PI, who will coordinate with other investigators to interview the subject and make a determination of need concerning specific medical care or removal from the study. Events of this type are uncommon, usually transient and pose minor barriers to the completion of this study. Participants may choose not to participate in any intervention activity that they find stressful. Awkwardness in discussing symptoms of OUD in a group setting may pose a barrier to sharing experiences for some participants, especially early in the study. Participants will be reassured that they are not required to share their personal experiences with the group. Moreover, participants will be asked to maintain the confidentiality of information disclosed in their MORE group. Participants may interpret MORE as a substitute for usual, conventional medical care. All participants will continue to receive the same medical care from their physician that they would otherwise receive. They will be informed that they should continue such care just as if they were not enrolled in a study. Participants will be asked to inform study personnel if there is a change in medications or other medical care during the trial (both during treatment and follow-up), but patients and their physicians will not be dissuaded from changing medical management practices.

The consent form will specify that it is the option of the PI and the research team to withdraw a subject from the study should they prove to be a danger to self or others, or a significant disruption to the group. If participants appear intoxicated (as determined by meeting DSM-5 diagnostic criteria for alcohol, cocaine, opioid, amphetamine, or hallucinogen intoxication) or actively psychotic or suicidal during study assessments or study treatment group sessions, they will not be allowed to continue that session. Instead, they will be referred to receive medical evaluation by a physician University of Utah Health. Alternatively, if the participant is determined to be a danger to self or others due to suicidal ideation or intoxication, police will be alerted. Afterward, the PI will contact the participant in question and interview them to determine whether their substance use or psychiatric symptoms warrant exclusion from the study.

12.5.1 Protection Against Risks

Minimizing Risks: Subjects will not be identified in any reports on this study. In the case of adverse effects or physical injury resulting from participation in these studies, subjects are provided with contact numbers for the PI and study physician and a 24-hour emergency access number to obtain immediate medical care. Records will be kept confidential to the extent provided by Federal, State, and local law. Nevertheless, subjects are informed that the sponsor and the Institutional Review Board for human subjects research may inspect the records of this investigation.

During study procedures, all participants will be monitored at all times by research personnel associated with the project (study coordinator, research assistant) or the investigators themselves. All the participants will have ready access to the phone numbers of the study coordinator and the responsible clinicians (Dr. Garland, Dr. Lewis, Dr. Thielking). Participants will be encouraged to contact the investigators if they notice any worsening of symptoms or untoward side effects. The investigators have ample prior experience in the utilization of these study procedures and patients will be routinely evaluated during the course of the clinical trial. The responsible clinicians (Dr. Lewis, Dr. Garland, Dr. Thielking) will be available by cell phone in case of unexpected adverse or symptom worsening.

Procedures for Protecting against Risk:

We have a robust protocol for managing adverse events associated with intramuscular (IM) ketamine administration, as detailed in the table below.

Ketamine Adverse Event Management

Adverse Event	Subject Management
Elevated BP	• Monitoring of vital signs at baseline, 40 minutes, and prior to departure. • Supportive care. MD supervision. • BP measurements that meet criteria for hypertensive urgency (>180/110) will be treated with clonidine 0.1mg-0.2mg with q15 minute BP checks.
Headache	• Subjects will be examined by a licensed physician and offered acetaminophen 650mg.
Nausea/Vomiting	• Subjects will be assessed by a licensed physician with an emphasis on the least invasive means, avoiding medication administration if possible. • If nausea/emesis is significant and subject requesting antiemetic, ondansetron 4mg-8mg will be provided (either SL or IM).
Acute anxiety, dysphoria, or paranoia	• Subjects will be offered supportive psychotherapeutic interventions by the therapist team. If this is insufficient with ongoing significant distress subjects will be offered 2mg lorazepam (either oral or IM).

Adverse Event	Subject Management
Other	• A licensed physician will examine the subject and determine the appropriate level of care for the subject.

Diphenhydramine Adverse Event Management

Adverse Event	Subject Management
Sedation	• Supportive care, MD supervision and monitoring. Medical clearance for departure from clinic.
Headache	• Subjects will be examined by a licensed physician and offered acetaminophen 650mg.
Nausea/Vomiting	• Subjects will be assessed by a licensed physician with an emphasis on the least invasive means, avoiding medication administration if possible. • If nausea/emesis is significant and subject requesting antiemetic, ondansetron 4mg-8mg will be provided (either SL or IM).
Acute anxiety or agitation.	• Subjects will be offered supportive interventions by the therapist team. If this is insufficient with ongoing significant distress subjects will be offered 2mg lorazepam (either oral or IM).
Dry eyes, dry mouth	• Hydration and OTC moisturizing eye drops available.
Constipation	• Evaluation on day following treatment. OTC stool softeners recommended if ongoing constipation.
Other	• A licensed physician will examine the subject and determine the appropriate level of care for the subject.

We have developed plans to minimize and manage unexpected clinical events, including emotional distress, suicidality, or medical instability. Additional protections against risk are as follows:

MORE Providers: The MORE clinician, a licensed psychotherapist with >5 years of experience providing mindfulness-based therapy for addiction will be trained in MORE by PI Garland. Dr. Garland will monitor fidelity using the MORE Fidelity Measure (Hanley & Garland, 2021), with feedback delivered in weekly supervision to maintain intervention integrity. MORE treatment sessions will be held via a HIPAA-compliant telemedicine platform.

Ketamine Providers: Dr. Lewis and Dr. Thielking are board-certified psychiatrists. They are both trained in ketamine-assisted psychotherapy through the Psychedelic Research and Training Institute (PRATI) with additional training in psychedelic assisted therapies through the California Institute of Integral Studies (CIIS) and the Multidisciplinary Association for Psychedelic Studies (MAPS). Dr. Lewis is the primary clinician responsible for ketamine administration but Dr. Thielking will also deliver ketamine sessions.

Adverse Event Reporting: All participants will be asked to record any adverse events and to report them to the therapists, physicians, and the study coordinator as soon as possible. In addition, they will be asked about their experiences at each study visit and at each treatment sessions. Participants will also be strongly encouraged to discuss with the research staff anything they feel to be an adverse event or other issues that are problematic about the study. Adverse events will be recorded and reported to the PI, co-investigators, and the University of Utah IRB.

Hence, several mechanisms will be in place to identify participants who may be experiencing potential adverse effects during the study: 1) communication between participants and the research staff; 2) direct, observation of participant's health status by the therapists and physicians; and 3) verbal inquiry concerning potential adverse effects through weekly review by the therapists while intervention sessions are going on.

Response to Adverse Events: In the event of a report of a possible adverse event, the adverse event will be assessed by Drs. Garland, Lewis, and/or Thielking to determine the relatedness and severity of the event as needed. The level of care will be determined and the participant referred appropriately for care, which may involve the resources of a primary care clinic, a hospital, or a psychiatric facility connected with the University of Utah.

Drs. Garland, Lewis, and/or Thielking, will provide advice with regard to the appropriate type of health care that the participant should seek, and help the participant access that level of care. If the MPIs, study physicians, or participant believes that a serious adverse event resulting from the study procedures has occurred, the PI will notify the University of Utah IRB within 24 hours. Further involvement in the study by that participant may be terminated.

Research Materials Handling: Confidentiality of all materials will be maintained by use of anonymous identification numbers on all data. All materials derived from the study will be handled only by study personnel during collection, storage, and in subsequent data analysis. The PI is experienced in conducting clinical studies and is fully aware of the need for anonymity, privacy and security, and will maintain strict surveillance of the office environment. No incidents of violation of patient confidentiality have occurred in the previous studies in which Drs. Garland has participated.

12.5.2. Potential Benefits of the Proposed Research to Participants and Others

The potential benefits of the research to the participants are significant. Their OUD symptoms, drug use, craving, comorbid mood and anxiety symptoms, or distress may improve significantly as a result of being part of the study. Opioid use reduction could reduce risk for opioid overdose. Insights from participation in MORE or ketamine treatments may be useful for participants to improve their health and overall quality of life. Research suggests that MORE may also be useful as an adjunctive treatment for a number of disorders associated with OUD that may be present in members of the study cohort. The process of participating in MORE + ketamine might also enhance self-efficacy and participants randomized to ketamine treatments may benefit in terms of symptoms of depression and anxiety. Therefore, it is expected that participants in both study arms may experience significant benefit from participating in the research study.

The potential benefits to other individuals with OUD are also significant. The results of this research may provide credible evidence about the effects of MORE + ketamine as a treatment for OUD, and whether these interventions may be usefully integrated with routine clinical care. Any evidence derived from this research suggesting that MORE + ketamine improves OUD outcomes may help other patients obtain relief through this approach. Information derived from this research suggesting that MORE + ketamine may not be useful for OUD will help patients and their health-care providers focus on treatment modalities that are more effective.