PROTOCOL TITLE: A Randomized, Placebo-Controlled, Double-Blind Study to Evaluate the Efficacy of Ketamine for the Treatment of Concurrent Opioid Use Disorder and Major Depressive Disorder

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TABLE OF CONTENTS

1. OBJECTIVES/SPECIFIC AIMS

1.1 Introduction and Context

Opioid use disorder (OUD) has rapidly become a public health epidemic despite existing opioid substitution pharmacotherapies. In 2016, an estimated 11.5 million Americans misused prescription opioids and 948,000 people used heroin, representing a 500% increase since 1999 (Centers for Disease Control, 2018). This is highly concerning, as opioids are responsible for over 2/3 of all drug overdose deaths and in 2017, one person died approximately every 11 minutes of opioid overdose (Centers for Disease Control, 2018). The high incidence of heroin use (there were 170,000 new heroin users in 2016) is also problematic given the risk of blood-borne infections including HIV and HCV (Health and Human Services, 2018). The opioid epidemic is overall estimated to cost 504 billion dollars annually (Council of Economic Advisors, 2017).

1.2 Description of Current Standard of Care

All currently approved pharmacotherapies for OUD act as either agonists (i.e. methadone), antagonists (i.e. naltrexone), or partial agonists (i.e. buprenorphine) at the mu-opioid receptor. Successful induction rates onto extended release opioid antagonist therapies such as monthly extended release naltrexone injection are low (40-46%, Bisaga et. al., 2018). Furthermore, rates of relapse at 24 weeks (defined 7 days of self-reported opioid use or 4 consecutive weeks of positive urine toxicology screens) are high for both monthly injections of extended release naltrexone (65%) and self-administered daily oral buprenorphine-naltrexone (57%, Lee et al., 2018). Similarly, comparisons of daily methadone vs buprenorphine found mean opioid relapse rates after 13 weeks of treatment of approximately 40%, with no between-group differences (Mattick et al., 2003). These findings suggest room for improvement using novel treatment approaches (Connery et al., 2015).

1.3 Purpose and Objectives of the Study

The primary objective of the proposed study is to directly address this critical need by preliminarily testing the efficacy of ketamine in reducing opioid use and depression symptoms among individuals (N=30) with concurrent OUD and MDD who have failed to maintain abstinence despite treatment with a standard of care pharmacotherapy for OUD (i.e. buprenorphine, methadone or naltrexone). Effects on related symptoms and psychiatric conditions (e.g., cravings, motivation to quit, and anxiety symptoms) will also be explored. To accomplish this, we will use an intent-to-treat, double-blind, randomized clinical trial to compare the efficacy of ketamine to placebo control over a twice-weekly treatment schedule for four weeks. We will examine standardized, repeated dependent measures of clinical outcomes at baseline and multiple time points after the first treatment (48h to 8 weeks post initial treatment) with primary outcomes assessed at one month following the first treatment.

1.4 Specific Aims

To achieve these objectives, the following Specific Aims are proposed:

Specific Aim 1: To demonstrate the feasibility of study recruitment and completion of the treatment protocol.

Specific Aim 2: To preliminarily assess the efficacy of ketamine, as compared to placebo, in reducing OUD severity (i.e., percent days using opioids, abstinence rates) as measured by the Timeline Followback and urine drug screen tests.

Specific Aim 3: To preliminarily assess the efficacy of ketamine, as compared to placebo, in reducing symptoms of depression using the Montgomery–Asberg Depression Rating Scale.

2.0 BACKGROUND

Role of Depression in Maintaining Abstinence From Opioids

Negative affect has been found to be a key mediator in failure to achieve abstinence and depression is a frequent comorbidity in OUD. Nearly two out of three persons entering treatment for opioid detoxification screen positive for depression, however 48% of those meeting criteria for depression had not perceived a need for treatment (Brienza et al., 2000; Stein, 2017; Volkow, 2004). However, desire for improvement in mood is the most commonly cited reason for relapse in OUD following initial addictions treatment (Kadam et al., 2017; Huhn et al., 2018; Volkow et al., 2019). In addition to contributing to relapse and being a risk for unintentional overdose, OUD is an independent risk factor for completed suicide (Volkow et al., 2019). A national cohort study of veterans (n=4,863,086) found that after controlling for psychiatric and medical comorbidities, overall substance use was still associated with a 1.67 hazard ratio for suicide in men and 2.15 in women (Bohnert et al., 2017). Furthermore, in women, OUD was associated with the highest hazard ratio for suicide of any substance of abuse at 2.33 (Bohnert et al., 2017).

Glutamatergic Dysregulation Contributes to Both Depression and Addiction Pathology

Glutamatergic dysregulation in the prefrontal cortex and mesolimbic regions (including the amygdala and the nucleus accumbens) has been implicated in addiction pathology across multiple substances of abuse (Gass & Olive, 2008; Markou et al., 1998). Similarly, depression has been shown to have aberrant glutamate signaling (Abdallah et al., 2017; Murrough et al., 2017; Niciu et al., 2014). On a cellular level, astrocytes are responsible for maintaining glutamate homeostasis (Parpura and Verkhratsky, 2012) and both depression and addiction have been linked to impaired ability of astrocytes to upregulate glutamate (Rajkowska et al., 2013; Scofield et al., 2014). Ketamine is a noncompetitive antagonist of NMDA glutamatergic receptors which has been widely used for pain control in conjunction with general anesthesia since it was FDA approved in 1970.

Clinical Trials for Depression Treatment

Results from several meta-analyses indicate that ketamine can induce ultra-rapid improvements in depression and suicidality (Han et. al., 2016; Wilkinson et. al., 2017). This remission is most enduring in individuals with a family history of substance use disorders (Niciu et al., 2014). It is widely accepted that all currently approved pharmacotherapy classes for depression (serotonin reuptake inhibitors, monoamine oxidase inhibitors, and tricyclic antidepressants) are associated with a delayed onset of anti-depressant activity of 2-4 weeks. A meta-analysis of nine high-quality studies showed that ketamine was significantly more effective than placebo in reducing symptoms of major depressive disorder at 24 hours, 72 hours, and 7 days post-infusion (Han et. al., 2016). Additionally, results from a recent meta-analysis of ten clinical trials showed accumulating evidence that ketamine can significantly reduce suicidal ideation within 24 hours with moderate to large effect sizes (Wilkinson et. al., 2017). The overall duration of anti-depressant response was found to last between 3-12 days (Andrade, 2017). However, in a subgroup analysis, positive family history of alcoholism was found to be associated with a significantly longer duration of anti-depressant efficacy, averaging 17 days for the family history positive group and 3.6 days for the family history negative group (Niciu et. al., 2014). This suggests that the genetics underlying substance use confer a stronger response to the effects of ketamine.

Clinical Trials for Substance Use Disorder Treatment

Ketamine has shown early evidence of efficacy in the treatment of substance use disorders. One study evaluating the adjunctive use of ketamine in heroin use disorder showed that a single-session of high-dose (2 mg/kg IM) ketamine demonstrated one-month abstinence rates of 85% compared to 55% abstinence in the low dose group (0.2 mg/kg IM), and one-year abstinence rates of 24% in the high dose group as compared to 6% in the low-dose control group (Krupitsky et al., 2002). In a follow-up study comparing three repeated sessions of ketamine infusions with concurrent psychotherapy to single-session treatment, abstinence rates were increased to 50% in the 3 session group as compared to the single session rate of 22% (Krupitsky et al., 2007). Related studies found that ketamine is useful as an adjunct to psychotherapy in the treatment of alcohol use disorder (Krupitsky and Grinenko, 1997) with

one-year complete abstinence rates of 65.8% in the ketamine-assisted psychotherapy group compared to 24% in the control psychotherapy group. Intriguingly, the anti-depressant response to ketamine occurs primarily after the drug has been cleared from the body, suggesting that its primary effects are mediated through downstream processes. Ketamine has also been shown in a randomized controlled trial to facilitate rapid-opioid induction under general anesthesia, with significant improvements in clinical and subjective opioid withdrawal symptoms (Jovaisa et. al., 2006). More recently, ketamine has been studied in cocaine use disorder and found to improve levels of motivation to quit using and to reduce cocaine craving (Dakwar et al., 2014) and reduce rates of cocaine self-administration by 67% relative to baseline (Dakwar et al., 2017; Dakwar et al., 2018). Ketamine has been studied as an adjunct agent to benzodiazepines for acute alcohol withdrawal and has been found to reduce supplementary diazepam equivalent requirements by 40 mg at 12 hours post-ketamine initiation while maintaining equivalent levels of withdrawal symptoms between groups (Wong et al., 2015).

Novelty and Importance of the Current Study

While non-controlled trials for heroin and small pilot trials for other substance of abuse have shown evidence that ketamine improves abstinence rates and motivation to quit while reducing cravings, there are no completed randomized controlled trials evaluating the efficacy of ketamine in increasing abstinence in OUD.

3.0 INTERVENTION TO BE STUDIED

3.1 Overview of Study Medication

Ketamine was originally FDA approved in 1970 for pain control in conjunction with general anesthesia (Ketalar, 2018). The drug has since been evaluated in academic settings for the treatment of pain and a multitude of psychiatric indications. Ketamine has been increasingly studied in academic settings and used off-label in private practice settings over the past 10 years (Wilkinson et al., 2017). Ketamine undergoes extensive hepatic first pass metabolism, with an oral bioavailability of approximately 16% (Mathew et al., 2012). For induction of anesthesia, doses of 1 to 4.5 mg/kg IV or 6.5 to 13 mg/kg IM are recommended (Ketalar, 2018).

3.2 Safety and Toxicity

The acute toxicity of ketamine has been studied in multiple species. In mature mice and rats, the intraperitoneal LD50 values have been shown to be approximately 100 times the average human intravenous dose (Ketalar, 2018). Repeated, daily intravenous injections have been studied in rats, and dogs for as long as 6 weeks with excellent tolerability (Ketalar, 2018). Similarly, twice weekly treatments in monkeys over a four- to six-week period were well tolerated (Ketalar, 2018). At sub-anesthestic doses in human clinical trials for depression, the most clinically significant physical adverse event from ketamine is a transient increase in blood pressure, which was experienced by 29.8% of participants with a mean systolic blood pressure increase of 19.6 mmHg ($p<0.001$) and a mean diastolic blood pressure increase of 13.4 mmHg ($p<0.001$, Wan et al., 2015). Small, but statistically significant changes in perception (including derealization, depersonalization, distortion of time and space, and sense of illusion) were categorized as “feeling strange or unreal” and were experienced by 11.7% of participants (Wan et al., 2015). The average peak score of 4.5 on the Brief Psychotic Rating Scale is consistent with very mild symptom severity (Wan et al., 2015).

3.3 Study Drug, Dose, Mode of Administration and Justification

Ketamine is concentrated at a dose of 50mg/ml and will be administered by intramuscular administration in the amount of 60 mg (1.2 ml). This dose follows the FDA-dosing guidelines of a maximum dose of 60 mg per treatment day, with a lifetime maximum of 8 treatments for psychiatric indications. Each study drug administration will be directly observed by the PI. For a 75 kg person, this dose will translate into an effective dose of 0.74 mg/kg based on an intramuscular bioavailability of 93%. While formal dose response studies for depression are lacking, ketamine has been most widely studied for psychiatric indications at 0.5 to 1.0 mg/kg given intravenously. Although there are only a few studies evaluating the use of ketamine in the treatment of substance use disorders, doses in these trials have ranged from 0.5 to 0.8 mg/kg given intravenously or 2 mg/kg given intramuscularly (Jones et al., 2018).

3.4 Placebo Drug, Dose and Mode of Administration

A visually identical sterile saline control injection of equal volume will be also administered intramuscularly.

4.0 STUDY ENDPOINTS

4.1 Primary Outcomes

Primary outcomes will be 1) the percentage of individuals completing informed consent out of the number of individuals eligible on the initial screening and 2) the percentage of individuals that complete informed consent which complete the full protocol.

4.2 Secondary Outcomes

Secondary outcomes will include changes in depression severity (as measured on the Montgomery–Asberg Depression Rating Scale), which will be calculated as a change from baseline to 4-week follow-up.

- Montgomery Asberg Depression Rating Scale (MADRS; Montgomery, 1979). The MADRS is a clinician administered, 10-item questionnaire of depression severity. The total score ranges from 0-60, with scores of 0-6 considered normal (non-depressed), 7-19 indicative of mild depression, 20-34 indicative of moderate depression, and 35-60 indicative of severe depression. Individuals scoring 20 or higher on the MADRS will be included in the study. The MADRS evaluates the following symptoms of depression: 1) clinical appearance of sadness, 2) self-reported sadness, 3) inner tension, 4) reduced sleep, 5) reduced appetite, 6) concentration difficulties, 7) lassitude, 8) inability to feel, 9) pessimistic thought process, and 10) thoughts of suicide. The MADRS has a sensitivity of 94% and a specificity of 83%, has been shown to have high internal consistency, and correlates well with other measures of depression such as the Hamilton Depression Scale.

4.3 Exploratory Outcomes

Exploratory outcomes will include changes in characteristics related to opioid addiction including percentage of days using opioids and abstinence rates (Timeline Followback), motivation to quit (University of Rhode Island Change Assessment), craving for opioids (Visual Analog Scale), and related areas of psychiatric functioning.

- Timeline Follow-Back (TLFB; Sobell & Sobell, 1992): The TLFB obtains retrospective self-report of substance use by using a calendar and memory prompts to stimulate recall. Quantity and frequency assessments are made using this instrument (e.g., total amount of opioids used, percent of days using) as well as abstinence (yes/no). TLFB yields consistently high test-retest correlations and correlates well with other self-reports and collateral reports. The TLFB will assess consumption of opioids for 60 days prior to study entry, during the interventional phase and the follow-up phase. Use of nicotine and other drugs of abuse, including prescription drugs, will also be assessed using the TLFB.
- Urine Drug Screen (UDS) tests: Urine samples will be tested with a Multi-Drug Panel Test, which allows for the detection of THC/Marijuana, Cocaine, Phencyclidine, Opioids, Methamphetamines, Amphetamines, Barbiturates, and Benzodiazepines.
- Saliva Drug Screen tests: For follow-up visits conducted by telehealth, a Multi-Drug Panel saliva drug screen test may be optionally used in place of urine tests to facilitate ease of testing in a home setting.
- University of Rhode Island Change Assessment Scale (URICA; DiClemente & Hughes, 1999): This 32-item, self-reported questionnaire uses a five point Likert scale to assess levels of motivation to change according to the transtheoretical model (Precontemplation, Contemplation, Action, and Maintenance). This will be measured as the level of motivation to make changes may be mechanistically related to improving in opioid use.
- Visual Analog Craving Scale (VAS; McMillan & Gilmore-Thomas, 1996). At baseline, during the interventional visits, and at each follow-up visit, patients will be asked to report on the frequency, duration, and intensity of their opioid cravings on a 10 point (100 mm) VAS. This approach has been shown to yield a reliable and valid measure of craving in previous research.

- Generalized Anxiety Disorder Screener (GAD-7; Spitzer et al., 2006). The GAD-7 is a 7-item self report instrument that will assess generalized anxiety symptomology.
- Five Facets of Mindfulness Questionnaire (FFMQ; Baers et al., 2006): The FFMQ assesses five components of mindfulness including observation, non-judgement of experience, non-reactivity to inner experience, acting with awareness, and description of experience.
- PTSD Checklist (PCL-5; Weathers et al., 2013): The PCL-5 is a 20-item self-report measure. The PCL-5 is similar in form to the PTSD Checklist (PCL) based on the DSM-5 (Weathers et al., 1993), which has excellent psychometric characteristics for screening and as a secondary indicator of PTSD symptom severity (McDonald & Calhoun, 2010).
- Insomnia Severity Index (ISI; Morin, 1993). The ISI is a 7-item, self-report measure that assesses perceived severity of insomnia. The items sum to produce a total score (range 0–28). The ISI has an internal consistency alpha coefficient of 0.74, and has shown convergent validity with other measures such as the Pittsburgh Sleep Quality Index and sleep diaries).
- Brief Pain Inventory (BPI; Cleeland, 1991). This 9-item questionnaire uses a 10-point Likert scale to assess the severity of pain and its interference on difference aspects of quality of life and function.

5.0 INCLUSION AND EXCLUSION CRITERIA/STUDY POPULATION

5.1 Initial Screening Methodology

Initial screening eligibility will be conducted by the PI or trained research personnel. Patients with a self-reported history of depression and opioid misuse or illicit opioid use for which they report being maintained on buprenorphine for at least thirty days will be eligible to complete informed consent and baseline evaluation.

5.2 Inclusion Criteria

A subject may be eligible for enrollment if all of the following inclusion criteria apply within the thirty days prior to randomization:

1. Between the ages of 18 to 65 years old.
2. Able to provide informed consent.
3. Meet DSM-5 criteria for Major Depressive Disorder, without psychotic features.
4. Score at least 20 on the Montgomery-Asberg Depression Rating Scale.
5. Fulfill a minimum of 4 of 11 current opioid use disorder criteria by DSM-5.
6. Have used opioids illicitly at least once in the past month.
7. Subjects must be on a standard of care pharmacotherapy for OUD (buprenorphine, methadone or naltrexone) for at least one month.
8. Subjects taking other psychotropic medications (e.g. anti-depressants or non-benzodiazepine anxiolytics) must be maintained on a stable dose for at least four weeks before study initiation.
9. Must consent to random assignment to ketamine or placebo control.

5.3 Exclusion Criteria

Patients will be excluded from the study if any of the following criteria apply:

1. They are considered an immediate suicide risk (by Columbia Suicide Severity Rating Scale of 4 or greater, a history of a suicide attempt in the past year, or by clinician judgment) or felt to be likely to require hospitalization during the course of the study.
2. They have a self-reported history of illicit ketamine use, or baseline urine drug testing positive for ketamine.
3. They are in acute opioid withdrawal (as evidenced by a score of 5 or above on the Clinician Opioid Withdrawal Scale). These subjects will be referred for clinical detoxification and pharmacotherapy induction. Subjects may be re-assessed for study eligibility after one month of treatment with a standard of care OUD pharmacotherapy.
4. Subjects who meet DSM-5 criteria for current bipolar disorder.
5. Subjects who meet DSM-5 criteria for current or history of psychotic spectrum disorders.

6. Women who are pregnant or nursing, and women who do not consent to use methods of highly effective birth control during the interventional phase of the study.
7. Subjects with current hypertension as defined by a systolic blood pressure (SBP) >140 mmHg or a diastolic blood pressure (DBP) >90 mmHg.
8. Subjects with a self-reported history of delirium for any cause.
9. A history of allergic or other adverse reaction to ketamine.
10. Clinically significant abnormal laboratory values, physical exam findings or self-reported medical conditions for which a transient increase in blood pressure could be significantly detrimental (e.g. glaucoma, brain aneurysms, cardiovascular disease, or end-stage renal disease).
11. Electrocardiogram (ECG) findings (obtained within thirty days prior to randomization) of tachycardia, prior myocardial infarction, myocardial ischemia, or aberrant conduction).

6.0 NUMBER OF SUBJECTS

Approximately 30 patients are planned for enrollment in this study with no gender, race, or ethnicity exclusions.

7.0 SETTING

All procedures will be conducted in private research study rooms on MUSC campus.

8.0 RECRUITMENT METHODS

A chart review will be conducted for research purposes. Potentially eligible patients will be identified. The potentially eligible patients in the PIs practice will be informed about the study as the PI feels is appropriate. Then potential patients who have agreed to be contacted for future research by logging their MUSC Research Permissions preferences in MyChart will be contacted by phone and invited to participate. All other patients will be contacted through their providers to be informed of the study if the provider feels it is appropriate.

Recruitment will also be conducted through online (i.e. Craigslist) and flyer advertisements throughout the hospital and outpatient clinics at MUSC and other local clinics providing OUD treatment.

9.0 CONSENT PROCESS

9.1 Qualifications of Study Personnel Obtaining Informed Consent and Capacity of Participants

The research team have completed (or will complete upon hiring) the Miami Collaborative IRB Training Initiative (CITI) course and its associated tests in research ethics. Only the PIs, or Co-I's will obtain informed consent.

9.2 Location of Informed Consent

Informed consent will be obtained at the study research offices, in a private and interruption-free environment.

9.3 Method of Obtaining Consent

Study personnel will ensure that the participant is given full and adequate written and verbal information about the nature, purpose, possible risks and benefits of the study. There will be no mandatory waiting period prior to obtaining informed consent, however participants will not be required to make a decision at the time of initial contact. Participants will also be allowed to discuss the study with family or other individuals prior to giving their informed consent. After participants have reviewed the informed consent document, participants will be asked to relay their understanding of key elements related to the study procedures (i.e. voluntary nature of participation, basic study visit procedures, duration of study, anticipated risks and benefits) to ensure their understanding of the study prior to obtaining informed consent. Consent content will be reviewed as necessary to ensure that subjects have an adequate understanding to provide initial and ongoing consent. The participant's signed and dated informed consent will be obtained before conducting any study tests or procedures that are not related to their

routine care. The Investigator will maintain the original, signed informed consent document. A copy of the signed informed consent document will be given to the participant.

9.4 Capacity of Participants to Give Informed Consent

No vulnerable populations (e.g. children, cognitively impaired individuals, incarcerated individuals, or pregnant women) will be included in the study, and informed consent must be obtained directly from the participants.

10. STUDY DESIGN/METHODS

10.1 Study Overview

This is a double blind, placebo-controlled trial to assess the efficacy and safety of twice weekly intramuscular injections of ketamine in decreasing symptoms of OUD and MDD. Subjects will participate in a baseline visit to complete informed consent as well as complete assessments to evaluate study eligibility and collect baseline data. Eligible participants will return within one week for the initial ketamine intervention procedure. Immediately prior to the interventional procedure, participants will be guided through a mindfulness-based exercise to facilitate relaxation and reduce anxiety during the intervention. Participants will be subsequently monitored for 120 minutes, during which time they will complete measures assessing their perception of the interventional experience. Participants initially assigned to the placebo group may choose to optionally complete 8 ketamine medication sessions beginning in Study WK #5.

Groups A & B			
Visit #1: Baseline Assessments			Study WK #0
Visit #2: 1st Tx	Visit #3: 2nd Tx		Study WK #1
Visit #4: 1st Tx	Visit #5: 2nd Tx		Study WK #2
Visit #6: 1st Tx	Visit #7: 2nd Tx		Study WK #3
Visit #8: 1st Tx	Visit #9: 2nd Tx		Study WK #4
Group A (Ketamine)	**Group B (Placebo): Optional Visits**		
Visit #10: 1 WK follow-up	Visit #10: 1st KET Tx	Visit #11: 2nd KET Tx	Study WK #5
Visit #11: 2 WK follow-up	Visit #12: 3rd KET Tx	Visit #13: 4th KET Tx	Study WK #6
	Visit #14: 5th KET Tx	Visit #15: 6th KET Tx	Study WK #7
Visit #12: 4 WK follow-up	Visit #16: 7th KET Tx	Visit #17: 8th KET Tx	Study WK #8
	Visit #18: 1 WK follow-up		Study WK #9
	Visit #19: 2 WK follow-up		Study WK #10
	Visit #20: 4 WK follow-up		Study WK #12

10.2 Duration of Intervention and Study

Participants will complete a total of 12-20 study visits (including baseline assessment) as shown in **Figure 1**. Intervention visits will occur over a 4-8 week period, with three follow-up visits completed over the subsequent four weeks.

10.3 Schedule of Assessments

The instruments to be used are standardized, have good psychometric properties, and are widely used. The schedule of study assessments is provided in **Table 2**.

Table 2: Schedule of Assessments

Instrument Name	Purpose	TIME POINT											
		Wk 0	Wk1 (Wk5)		Wk2 (Wk6)		Wk3 (Wk7)		Wk4 (Wk8)		Wk 5 (9)	Wk 6 (10)	Wk 8 (12)
		BL	Tx1	Tx2	Tx3	Tx4	Tx5	Tx6	Tx7	Tx8	1W F/U	2W F/U	4W F/U
Self-Reports and Consent													
Informed Consent	Obtain informed consent	X											
Demographics Form	Sample characterization	X											
Concurrent Medications Form	Monitor medications	X	X	X	X	X	X	X	X	X	X	X	X
Treatment Services Tracking Form	Assess treatment engagement	X	X	X	X	X	X	X	X	X	X	X	X
*Time Line Follow-Back (TLFB)	**Primary Outcome:** opioid use (amt. and frequency)	X	X	X	X	X	X	X	X	X	X	X	X
Beck Depression Inventory-II	Self-reported assessment of depression symptom severity	X	X	X	X	X	X	X	X	X	X	X	X
Visual Analog Scale (VAS)	Measure subjective levels of opioid craving	X	X	X	X	X	X	X	X	X	X	X	X
General Anxiety Disorder (GAD-7)	Self report of anxiety symptom severity	X	X	X	X	X	X	X	X	X	X	X	X
Mystical Experiences Questionnaire	Measure of perceptual experiences		X	X	X	X	X	X	X	X			
Brief Pain Inventory	Measure of pain and quality of life	X		X		X		X		X			X
University of Rhode Island Change Assessment (URICA)	Measure of motivation for change	X		X		X		X		X			X
Insomnia Severity Index (ISI)	Assess insomnia and sleep quality	X		X		X		X		X			X
Five Facets of Mindfulness (FFMQ)	Assess aspects of mindfulness related	X		X		X		X		X			X
PTSD Checklist (PCL-5)	Measure of PTSD symptoms	X		X		X		X		X			X
Fagerstrom Test of Nicotine Dependence (FTND)	Measure of nicotine dependence	X		X		X		X		X			X
Assessment of the Blind	Participant Perception of Randomization									X			
Study goals	To characterize goals for treatment	X	X	X	X	X	X	X	X	X			
Clinician Assessments													
History and Physical Exam	Eligibility assessment	X											
Vital Signs Measurement	Obtain readings of blood pressure, pulse, temperature, respirations and pulse oximetry	X	X*	X*	X*	X*	X*	X*	X*	X*	X	X	X
Modified Observer Alertness/Sedation Scale (MOASS)	Measure of sedation		X	X	X	X	X	X	X	X	X		
Clinical Opioid Withdrawal Scale (COWS)	Clinician assessment of opioid withdrawal symptoms	X											
*Montgomery-Asberg Depression Rating Scale (MADRS)	**Primary Outcome:** Clinician assessed measure of depression symptom severity	X		X		X		X		X	X	X	X
Columbia Suicide Severity Rating Scale	Assess for presence and severity of suicidal ideation	X											
Mini International Neuropsychiatric Interview	Assess for psychotic spectrum and bipolar disorder, presence and severity of OUD	X											
Pre-screening Questionnaire	To assess for basic eligibility criteria before completing a full baseline visit.	X											
Laboratory and Procedural Tests													
Pregnancy Test (female participants only)	Eligibility assessment		X	X	X	X	X	X	X	X			
Drug Screen	Eligibility assessment (benzos), secondary outcome measure		X	X	X	X	X	X	X	X	X	X	X
Serum blood tests (CBC, CMP)	Assessment of hemodynamic, hepatic, and renal function	X**											
Electrocardiogram (ECG)	Assessment of cardiac function	X**											

* Vital signs (blood pressure, pulse, and respiratory rate) will be obtained prior to treatment sessions, and at 45 and 90 minutes post-treatment. Pulse oximetry will be monitored immediately prior to treatment, and for 90 minutes after treatment. If there is an increase in systolic or diastolic blood pressure >30 mm Hg from baseline, or an increase in pulse rate >30 bpm from baseline, the measurements should be repeated after the patient has been in a resting position for 10 minutes. ** Will be performed for individuals with significant prior cardiac, renal or liver diseases.

10.4 Baseline Assessment Procedures

After completing study informed consent, participants will undergo a comprehensive evaluation to assess for inclusion and exclusion criteria. This will include self-reports, clinician assessments, and laboratory tests as shown in Table 1. This will include assessment of depression severity, and participants at highest risk for suicidality will be excluded. The comprehensive exam will also include a history and physical exam by the study PI (pulse oximetry measurements will be a component of the respiratory evaluation), baseline medication evaluation for potential harmful interactions, laboratory panels (including assessment of renal and hepatic function), and electrocardiogram to ensure safe study participation. Baseline assessments may be conducted by telehealth with vital signs to be provided by participant's home or pharmacy measurement.

10.5 Method and Administration of Randomization

Randomized permuted blocks will be employed to obtain balanced randomization sequences for the two groups. The PI will be blinded to the randomization sequence and communicated to a designated pharmacist who not involved in clinical management of participants in order to preserve the double-blind design. The randomization assignment of participants will be carried out by this pharmacist

10.6 Intervention Visit Procedures

Prior to administration of the study compounds, participants will complete self-report questionnaires, urine testing, and clinical assessments. They will subsequently complete a 10-minute mindfulness-based psychological relaxation exercise and fill out a questionnaire regarding their study goals. Participant will be asked to disinfect their shoulder using an alcohol wipe, and the study physician will then administer the medication by intramuscular administration into the participant's deltoid muscle. Vital signs will be monitored prior to treatment, and at 45 and 90 minutes post-treatment, and blood oxygen levels will be continuously monitored using pulse oximetry. If during the post-administration observation period, ketamine administration causes an increase in systolic or diastolic blood pressure >30 mm Hg from baseline, or an increase in pulse rate >30 bpm from baseline, the measurements should be repeated after the patient has been in a resting position for 10 minutes. If the criterion is still met, then that patient will not receive further administration of ketamine and will be withdrawn from the study. After completion of the injection, participants will be monitored for 120 minutes, during which time they will undergo debriefing and complete assessments of their perceptual experience of the intervention. We will evaluate the effects of a twice weekly interventions for 4 weeks, and monitor outcomes over an additional 4-week follow-up period to inform pharmacotherapy frequency in future clinical trials. Follow-up visits may be conducted by telehealth.

11.0 SPECIMEN COLLECTION AND BANKING

Data will be in the form of self-reported questionnaires, medical record review (including labs and pertinent medical history for the purpose of eligibility clarification), urine and breath samples, physical exam and electrocardiogram and structured clinical interviews conducted by the PI. This data will be obtained specifically for research purposes. No biologic specimens will be stored for future use. Serum based laboratory tests (complete blood counts, complete metabolic panels) and electrocardiograms will be conducted using MUSC's clinical laboratories with test results entered into the participant's electronic medical record.

12.0 DATA MANAGEMENT

12.1 Data Analysis Plan

Baseline demographic characteristics will be collected and descriptive statistics will be used to characterize participants. Data will be collected and managed using the secure REDCap (Research Electronic Data Capture) database. Descriptive statistics for primary outcomes will include 1) the percentage of individuals completing informed consent out of the number of individuals eligible on the

initial screening and 2) the percentage of individuals that complete informed consent which complete the full protocol. Other descriptive statistics for the sample population will be analyzed, and baseline characteristics that are found to be significantly associated with other outcome measures will be included as covariates. Spaghetti plots will be produced to guide modeling outcomes as a function of time. All analyses will be conducted based on intention to treat. Subjects assigned to Group B (placebo) who complete Study Wk4 (at which time main outcomes are assessed), may choose to receive 8 ketamine treatments before completing follow-up visits. To preserve study blinding, subjects who are among the final 6 subjects being enrolled will not be unblinded until primary outcomes are assessed for all 30 subjects.

12.2 Hypotheses for Analyses

Feasibility Hypothesis: From the cohort of individuals completing the initial prescreening assessment, a 75% study enrollment rate will be deemed feasible. Therefore, we anticipate that 40 individuals will be needed to complete prescreening so that 30 participants will enroll in the study. Of the individuals enrolling in the study, we anticipate 60% of participants will *complete* the study protocol. *Completion* is defined for the study purposes as completing at least 75% of the study visits.

Hypothesis 1: Ketamine will result in significantly greater reduction in depression symptoms as compared to placebo at one-month. To test this hypothesis, we will employ repeated measures ANOVA using linear mixed models approach to assess reduction on the total score of the MADRS.

Hypothesis 2: Ketamine will result in significantly greater reduction in frequency of opioid use as compared to placebo at one-month. To test this hypothesis, we will treat the percent days using opioids (TLFB) as a continuous variable and analyze using linear mixed models approach. Abstinence at one-week (on UDS) will be compared by intervention groups using logistical regression analyses. An arcsine square root or logit transformation may be considered to stabilize variance of the proportions.

Hypothesis 3: Response to ketamine will be influenced by changes in motivation to quit (URICA) and qualities of psychoactive perceptual experience (HMS). To test this hypothesis, we will employ repeated measures ANOVA using linear mixed models approach.

Alternate Approaches: Diagnostics of the residuals will be performed to test the assumptions of the analysis. If the assumptions are found to be inadequate, alternative methods of analysis (e.g. ordinal logistic regression or Poisson regression) will be considered.

The primary dependent variables in all three analyses will be intervention group (ketamine or placebo), time (number of days), and the interaction between the two. Main hypothesis of interest will be the interaction and the post-hoc comparison at the one month after the first intervention. We anticipate the study population to include participants that are currently on antidepressants as well as those that are not. We considered stratifiying randomization by this variable, however since the proporption of participants on antidepressants at baseline is expected to be small, this will be considered as an independent variable in the statistical analysis. To account for within subject correlations, several structures, such as spatial autocorrelation (to accommodate unequal time points), and AR(1) symmetry, will be examined. Diagnostics will be performed to test the assumptions of normality and if found inadequate, appropriate transformations will be considered. An arcsine square root transformation may be considered to stabilize variance of the proportions. In all of the analyses, covariates will be considered to examine mediations. In a secondary analysis based on the spaghetti plots, we will consider linear and non-linear models of outcomes as a function of time. Specifically, over the 8-week follow-up period, we will examine if there exists a threshold point in time where the effect of ketamine plateaus. To achieve this, treating the joint-point as unknown, we will fit segmented regression models using non-linear mixed models.

12.3 Justification of Sample Size

For a 75% anticipated enrollment rate from the initial prescreened sample of 40 individuals, feasibility can be estimated within a margin of error of 14% with 95% confidence. Similarly, assuming a 60% rate of study enrollment of eligible participants, with a sample size of 30 we can estimate feasibility within a 17% margin of error with a 95% confidence interval. This study is powered to estimate the effects of ketamine on significant reduction in MADRS symptoms at the end of one month (see Hypothesis 1). Over the course of a two-year study, we estimate that we will be able to recruit 15 patients in each of the two intervention arms (2/month over 15 months). At 80% power, this sample size will allow us to detect a minimum difference in MADRS scores of 14.4 at one month between the ketamine and the placebo groups in a study design with 7 repeated measurements having a AR(1) correlation of 0.9, and a standard deviation of 15.8, with a significance level of 0.050 (Singh et al., 2016; Niciu et al., 2014). While we will examine changes in depression severity as a continuous variable, we will also examine other clinically accepted changes in depression severity such as response (defined as a 50% reduction in symptom severity from baseline) and remission (defined as below the threshold for mild depression which is a score of 6 on the MADRS). Baseline averages for the MADRS scores for this population will be assumed to be 34 (Niciu et al., 2014; Han et al., 2016; Singh et al., 2016). The minimum difference in MADRS of 14.4 is anticipated to be approximately 50% of the baseline measurements. Although there is limited information on the effectiveness of ketamine in the treatment of addiction, a sample of 30 subjects (15 in each arm) will provide adequate power to detect an 22% difference between the two groups in the percent of days abstinent from opioid use using the same longitudinal design as described above with 7 time points (Hypothesis 2). For this calculation, we assumed an AR(1) correlation of 0.9 and a standard deviation of 25% at a significance level of 0.05; an arcsine transformation was used for variance stabilization. Over the 8-week follow-up period, we will examine if there exists a threshold point in time where the effect of ketamine plateaus. To achieve this, we will use a segmented regression analysis using non-linear mixed models. We will take all efforts to keep dropouts to a minimum. However, our past experience suggests the rates of dropout are up to 20%. This could reduce the sample size per group to 12 and 12. The corresponding differences we could detect would be a minimum MADRS score difference of 16.1 and a 26% difference between groups in terms of the percent of days abstinent from opioid use. No interim analyses are planned.

12.4 Data Confidentiality Procedures

We will take rigorous precautions to maintain confidentiality for all participants, using procedures that the PI and her mentors have successfully employed in similar previous, as well as ongoing related studies. All study data related to mental health outcomes (i.e., the participant responses to questionnaires) and demographics will not have any unique identifying data attached. There will be only one master list of participants (not linked to participant responses). This list will be kept locked separate from other data and will be available only to the PI, her mentors, and approved study personnel. All data will be confidentially stored (i.e., in locked files or on encrypted servers) so as to protect the confidentiality of participant information. Access to research records (paper and computerized) will be restricted to the project staff, and to sponsor audit personnel and MUSC IRB auditors when indicated. All study personnel have completed (or will complete upon hiring) a certified program of instruction in the protection of human subjects in research, such as the University of Miami CITI course. These courses in the responsible conduct of research and the protection of human subjects will be completed on an annual basis, in compliance with MUSC regulations.

12.5 Data Quality Control Procedures

Data quality will be monitored by random inspection of the completed forms by the study team and any irregularities or problems detected will be discussed with the PI. At its discretion, the Sponsor or its designee may conduct a quality assurance audit of this study. Auditing procedures of the Sponsor and/or its designee will be followed in order to comply with GCP guidelines and ensure acceptability of the study data for registration purposes. If such an audit occurs, the Investigator will give the auditor direct access to all relevant documents, and will allocate his/her time and the time of his/her staff to the auditor as may be required to discuss findings and any relevant issues.

12.6 Study Documentation and Data Handling

Any clinical study event that is judged to be an AE will be recorded on the AE form during the course of the study. The PI and/or trained Research Assistant will ensure this information is captured during every study visit. Whenever a study participant has reported an AE, the study coordinator will discuss the event immediately with the PI (if possible while the study participant is there) who will evaluate the event. If the AE is not serious, the information will be recorded, managed medically as appropriate, and the event will be followed until resolution. SAEs will also be recorded on the AE Form, managed medically as appropriate, and the event is followed until resolution. In addition, the PI will review all completed AE forms for determination of SAE that require reports to the Sponsor. The PI will inform the Sponsor immediately of knowledge of a SAE. All information available on the event (hospital records, lab tests, discharge summaries, etc.) will be forwarded to the Sponsor so they can determine whether the SAE is unexpected or associated and the reporting outcome of the SAE. As additional information becomes available on the SAE, it will be forwarded to the Sponsor. All SAE reports will be sent to the MUSC IRB within 24 hours of learning of event occurrence.

AEs/SAEs will be documented and reported as per IRB requirements. Research staff will identify AEs and obtain all available information to assess severity, seriousness, study relatedness, expectedness, outcome and the need for change or discontinuation in the study intervention. Adverse events will be documented on AE Logs and additional relevant AE information, if available, will be documented in a progress note in the research record as appropriate to allow monitoring and evaluating of the AE. If the AE meets the definition for Serious, appropriate SAE protocol specific reporting forms will be completed and disseminated to the appropriate persons and within the designated timeframes as indicated above. For each AE/SAE recorded, the research staff will follow the AE/SAE until resolution, stabilization or until the participant is no longer in the study. When a reportable SAE is identified, the research assistant will initiate an SAE form, and the following individuals will be notified within 24 hours of the site's initial notification of the SAE:

1. The PI (Dr. Jones) will provide oversight, consultation, assessment and documentation as appropriate of the SAE.
2. The research staff will notify the MUSC IRB, and complete the AE report form in conjunction with the PI. Both committees meet monthly. Communication with the MUSC IRB is through email, memos, official IRB forms, and online reporting.
3. The data safety monitoring board members.

If complete information is not available when the initial 24-hour SAE report is disseminated, follow-up information will be gathered to enable a complete assessment and outcome of the event. This information may include hospital discharge records, autopsy reports, clinic records, etc. The research staff will attach copies of source documents to the SAE report for the PI and for forwarding to the sponsor as appropriate. All deaths that occur during the study or 30 days post termination from the study are required to be reported as adverse events even if they are expected or unrelated. Other adverse events are reportable to the MUSC IRB if the AE is unexpected AND related or possibly related AND serious or more prevalent than expected. All three criteria must be met for an AE to be reported to the MUSC IRB. The IRB definition of unexpected is that the AE is not identified in nature, severity or frequency in the current protocol, informed consent, investigator brochure or with other current risk information. The definition of related is that there is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention.

12.7 Privacy Protection and Confidentiality Assurances

While absolute confidentiality cannot be guaranteed, every possible effort will be made to protect the privacy of study participants, and all of the investigators have an excellent history of maintaining patient privacy and data security. Participants will be provided with a written informed consent document which specifies the risks and confidentiality protections and limits of study procedures. Subject names will remain confidential and all study data related to outcomes (i.e., the participant responses to questionnaires) and demographics will not have any unique identifying data attached in any way. There will be only one master list of participants (again, not linked to any participant responses) which will be

kept locked separate from all data and will be available only to the PI, Co-Is and approved study personnel. All data will be stored in a confidential manner (i.e., in locked files or on encrypted computers) so as to protect the confidentiality of participant information. Access to research records (paper and computerized) will be restricted to the project staff. Access to de-identified study data will be limited to named project investigators, sponsor audit personnel, and MUSC IRB auditors.

12.8 Data Sharing

The data collected from study participants, including PHI, will be entered into and securely stored in the database on a secure server by a member of the research study team. Electronic data will be stored, managed, and analyzed by the study PI and her statistical advisor.

13.0 PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS

Ongoing Clinical Monitoring: The research team will closely monitor for any increase in substance use or psychiatric distress at every study intervention visit. Subjects with clinically significant worsening of depression (i.e. development of suicidal ideation) or worsening of opioid use will be immediately referred for a higher level of treatment, and the DSMB will alerted within 48 hours to review trial safety. Mental health symptoms will be monitored using standardized measures at each visit in order to detect any worsening symptoms. Additionally, participants will be advised to observe any signs of worsening substance use or depression symptoms, and to discuss these with the research team. All participants will be informed at the initial visit that they may terminate participation at any point. If a participant experiences distress or other problems between visits, he or she will be encouraged to Dr. Jones or his/her outpatient mental health provider. If a participant needs or desires immediate attention, arrangements will be made for an appointment with an experienced mental health provider. The informed consent document will provide direction to contact the study staff during office hours and/or go to the Emergency Room at any time for worsening of symptoms. In addition, participants will have access to urgent care services at MUSC. If any of the research personnel believes that a participant is medically or psychiatrically compromised by participation, the PI will be notified and will contact the participant immediately to assess concerns and assure participant safety. The PI will attempt to address all participant concerns and will set up an alternate referral for counseling for those who desire it from outside the project. All participants will review, at the initiation of participation, an informed consent document which specifically reviews potential psychological distress as a potential outcome of participation. If necessary, the participant will be asked to complete a safety plan and to call the project staff, a national hotline, or 911. The Mobile Crisis unit of Charleston County, which involves a team of police and psychiatric workers, or the EMS unit may be dispatched to the participant's home to assure safety. The investigative team has a long history of ensuring participant safety using similar methods in these populations.

Pre-Intervention Assessment: A comprehensive exam will be conducted as part of the baseline assessment to minimize risks from study participation. This will include assessment of depression severity, and participants at highest risk for suicidality will be excluded. Participants will also be required to be in buprenorphine treatment for at least a one month period prior to study participation. The comprehensive exam will also include a history and physical exam by the study PI (pulse oximetry measurements will be a component of the respiratory evaluation), baseline medication evaluation for potential harmful interactions, and electrocardiogram to ensure safe study participation.

Peri-Intervention Monitoring: Subjects will be continuously medically and psychiatrically monitored throughout the course of the intervention and for a minimum of two hours after (or until any distress or dissociative symptoms reach clinically insignificant levels, and blood pressure returns to within 20% of their baseline values). Subjects will be instructed not to eat for at least 2 hours before taking the intervention sessions and not drink liquids at least 30 minutes after the intervention sessions to reduce the risk of nausea and vomiting. Emergency services will be immediately and continuously available on MUSC premises in the event of any medical complications. Subjects will not be allowed to drive themselves after the interventional visits, and alternative transportation will be arranged if needed.

14.0 WITHDRAWAL OF SUBJECTS

All potential participants will be thoroughly screened for eligibility after completing informed consent. The PI may withdraw subjects from participation at any time if the participant demonstrates or reports significant distress, is felt to be at risk of harm to themselves or to others, or is otherwise unable to complete the study protocol. Referrals to university and community resources will be made as indicated for all participants withdrawn from the study. The trial will be stopped under any of the following conditions: 1) there is clear evidence of harm; 2) there is no likelihood of the intervention demonstrating benefit, or 3) there is overwhelming evidence of the benefit of the intervention.

15.0 RISKS TO SUBJECTS

15.1 Overview

All medications have potential side effects. Ketamine has been well studied since its FDA approvals in 1970. Based on extensive prior research with intravenous ketamine in the treatment of depression, the prevalence of the most commonly observed adverse reactions are estimated below by category. Participants will be informed of all potential side effects associated with ketamine before study participation, and will be closely monitored both during the treatment and at each follow-up visit.

15.2 Physical Risks

The most clinically significant physical adverse event from ketamine is a transient increase in blood pressure, which in previous studies was experienced by 29.8% of participants with a mean systolic blood pressure increase of 19.6 mmHg +/- 12.8 mmHg ($p<0.001$) and a mean diastolic blood pressure increase of 13.4 mmHg +/- 9.8 mmHg ($p<0.001$) with peak levels reached on average at 40 minutes post-treatment and resolving by 240 minutes post-treatment (Wan et al., 2015). Participants experiencing clinically significant hypertension (greater than 180 mmHg SBP or greater than 105 mmHg DBP) will be treated with standard of care hypertensives (e.g. clonidine) and monitored until symptom resolution.

The most prevalent physical adverse effect was an increase in sedation (level of alertness) and is estimated based on previous studies to occur in approximately 16% of patients receiving ketamine. Sedation will be monitored using the Modified Observer Alertness/Sedation Scale (MOAA/S) at baseline, 40 minutes and 1.5 hours post medication administration. While ketamine is not associated with respiratory depression, continuous pulse oximetry will be monitored for a minimum of 1.5 hours post medication administration, or until resolution of sedation. A medical emergency team will be called for participants that are unable to be aroused with painful trapezius squeeze (MOAA/S score of 0) or that experience hypoxia (i.e. a pulse oximeter reading of 92% or less). Due to cognitive impairment associated with this transient increase in sedation, participants will not be allowed to drive themselves following the interventions, and will be advised not to operate heavy machinery for at least 24 hours after the interventions.

There are also the standard risks associated with intramuscular injections. These include temporary local pain, irritation, or redness at the site of the injection. There is a very small (<1%) risk of infection, muscle fibrosis, or persistent muscle or nerve damage at the site of injection.

15.3 Psychological Risks

The most clinically significant risks of ketamine in previous clinical trials include dissociation (including derealization and depersonalization) and perceptual changes (e.g. distortion of time and space, sense of illusions). These effects are estimated based on prior studies to occur in 42% of subjects receiving ketamine. Anxiety is estimated to occur in 15% of subjects receiving ketamine. Psychological distress will be minimized with pre-treatment relaxation exercises and psychological reassurance as needed. Psychological distress will be minimized with pre-intervention relaxation exercises and psychological reassurance as needed. In prior trials with ketamine for depression, these measures are sufficient to manage dissociation and anxiety in the overwhelming majority of participants. However, standard of care medications for agitation associated with delirium or psychotic symptoms (e.g. lorazepam) will be available in the event that participants develop severe anxiety psychological distress lasting longer than thirty minutes. Psychiatric hospitalization will be arranged if needed, in the unlikely event of severe or prolonged psychiatric symptoms (e.g. lasting greater than four hours or the business day). Participants

may also have emotional distress from answering the questionnaires, although this is mild in the investigators' experience with these instruments.

15.4 Abuse Liability

Ketamine is a psychoactive substance, and consequently has abuse liability. Ketamine is classified as Schedule III controlled substances (CIII). While there have been no randomized controlled trials evaluating the risk of subsequent illicit or recreational use of ketamine following medical administration (either for induction of sedation in conjunction with general anesthesia or in monitored off-label use for depression or pain management), in the extensive sub-anesthetic trials of ketamine for depression, there have been no published reports of illicit use developing after initial medical treatment with ketamine. None of the previous studies using ketamine in the treatment of substance use disorders reported illicit ketamine use following the ketamine interventions (Jones et al., 2018). While national statistics on ketamine are not collected, overall use prevalence rates for the entire hallucinogen classification (which includes ketamine) are estimated at 0.3% (Center for Behavioral Health Statistics and Quality, 2018). Animal models using intracranial self-stimulation have demonstrated that ketamine fails to progress to self-administration, also suggesting a lack of abuse liability (Hillhouse et. al., 2014). Globally, the World Health Organization (WHO) evaluates the overall risks and abuse liability of ketamine; in their most recent report, the WHO affirmed that ketamine does not pose a global health risk, and again recommended its continued use (WHO, 2015). Substance use will be assessed at each visit throughout the study, and participants will be referred for ongoing care if they develop worsening substance use. If participants report illicit use of ketamine between intervention sessions, they will be withdrawn and referred for substance abuse treatment.

15.5 Social Risks: Adverse social consequences may arise if the participants' medical history or psychiatric history (including substance use history as well as psychiatric comorbidities) are inadvertently communicated to others.

15.6 Legal Risks: Legal risks may arise if individuals are homicidal or suicidal and make these intentions known to the PI project staff, who may then be required to notify authorities and the target of homicidal intent. There is also a legal and physical risk if participants were to drive or operate heavy machinery while cognitively impaired (which may occur if they use opioids or as a result of the intervention).

15.7 Economic Risks: Subjects will be compensated for study participation as well as for any medical care related to study-related injuries.

15.8 Other Risks: While every possible effort will be made to protect the privacy of study participants, there is a risk of loss of confidentiality. There is also a risk of being randomized to the placebo intervention as opposed to the ketamine. There may also be unknown risks associated with the study procedure or intervention.

16.0 POTENTIAL BENEFITS TO SUBJECTS OR OTHERS

16.1 Potential Benefits to Subjects

Potential benefits of participation in this study may include a reduction in OUD and depression symptoms. Participants may also gain diagnostic information about their medical or psychiatric comorbidities, although this is not guaranteed. Overall, there is no guarantee or promise that participants will receive any benefit from participation in this study.

16.2 Justification of Risks

The potential benefits of the knowledge to be gained from the proposed study are considerable. This study proposes to test intamuscular ketamine in the treatment of co-occurring OUD and MDD among participants. The plans for monitoring risk as described above warrant the conduct of this study for the knowledge that may reasonably be expected to result.

17.0 SHARING OF RESULTS WITH SUBJECTS

The data collected from study participants, including PHI, will be entered into and securely stored in the database on a secure server by a member of the research study team. Electronic data will be stored,

managed, and analyzed by the study PI and a statistical mentor advisor. Individual baseline data may be released to participants on request for their subsequent medical use or disclosure.

18.0 DRUGS OR DEVICES

The IND application for ketamine's use in this study will be submitted by Dr. Jones for FDA review. Medication and placebo will be stored in lock boxes on the MUSC campus and be administered by the participant under the direct supervision of the PI.

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