Medical University of South Carolina
CONSENT TO BE A RESEARCH SUBJECT

TITLE OF RESEARCH: Ketamine-assisted psychotherapy for the treatment of persistent depression in abstinent opioid users

Concise Summary

Your consent is being sought for a research study. Participation is voluntary. The purpose of the study is to examine whether an investigational medication called ketamine along with psychotherapy can improve depression in individuals with past opioid addiction who have achieved sobriety for 3 months or more. If you are eligible and you decide to participate in the study, your participation will last approximately 16 weeks or 4 months.

The study will involve an initial screening visit. You will complete questionnaires and interviews in a private room. The questionnaires and interviews will be related to your physical and mental health. The initial phase of the study will involve 8 weekly clinic visits. At each of these visits, you will be asked to answer several questionnaires and women will provide a urine sample to check for pregnancy. You will meet with our therapist to set goals or intentions for each session. You will then be administered the study medication by an injection into your shoulder muscle and will be monitored by a study clinician until you feel back to your usual self. Our clinician therapist will be available during and after treatment to discuss your experience. You will also meet with our study physician 1, 2, 4, and 8 weeks after your final medication session. These follow-ups can be completed virtually (*ie*, via secure video software).

There are risks of participating in the study that are described in this document. The most significant risks include temporary high blood pressure, anxiety, and having the sensation that you are detached from your body or having an altered perception of time or your body. There is also a risk of loss of confidentiality, although steps will be taken to minimize this risk. Because it is not known if the study medication is safe in pregnancy, if you are a woman, you will complete a pregnancy test at each visit when medication is to be taken to be sure that you are not pregnant.

Your potential benefits from participating include improvement in your symptoms of depression. Your alternative is not to participate in the study. Alternative treatments are available for individuals with symptoms of depression who have opioid use disorder including medications such as sertraline, fluoxetine and citalopram as well as therapy or counseling.

A. PURPOSE OF THE RESEARCH

You are being asked to volunteer for a research study. Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making you decision. As the study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand.

The purpose of this study is to examine the ability of a medication called ketamine to reduce the severity of depression in people with a history of opioid addiction who are in recovery (also called opioid use disorder in remission). Ketamine is currently approved by the Food and Drug Administration (FDA) to reduce pain during some surgeries. However, ketamine is considered "investigational use" in this study, meaning that the FDA has not approved it for the treatment of either opioid addiction or depression. This is a Phase II study of ketamine, meaning that it has established use for other purposes and researchers are now testing this medication in larger populations. The purpose of this study is to evaluate the safety and effectiveness of ketamine in the treatment of depressed individuals with a history of opioid addiction. You are being asked to participate because you are over 18 years of age, you have symptoms of depression, and you have opioid use disorder with at least 3 months of sobriety.

This study is being conducted at MUSC in Charleston, SC and will involve approximately 10 participants.

B. PROCEDURES

If you agree to be in this research study, the following will happen:

1. Screening and Baseline Visit (approximately 2-3 hours in length):
   - The initial visit will involve the following:
     - Completion of written questionnaires related to your mental and physical health. Questionnaires will also be related your previous use of alcohol and other drugs, your craving levels for opioids, ways in which opioids has impacted your life (such as legal trouble or relationship conflicts) and your personal goals regarding your opioid use and depression.
     - An interview with a clinician about questions related to your physical and mental health.
     - A basic physical exam like what you would get at a checkup. Your blood pressure, pulse, and temperature may be checked at a local pharmacy or by a home measurement device.
     - If you have a history of heart problems or are taking methadone, you may be asked to complete an electrocardiogram (EKG). This is a test of the function of your heart and involves placing small adhesive pads with wires attached on your chest. After the adhesive pads are placed, a monitor shows a picture of the electrical activity of your heart, which is printed out on paper. This test usually takes less than 10 minutes to complete. If you have had this test done within the previous sixty days at MUSC, your

medical record will be reviewed. If this test was normal, you will not have to complete the electrocardiogram test.

- If you have a history of liver, kidney, or blood cell-related problems, you may be asked to have your blood drawn. Approximately 1 teaspoon of blood will be drawn for these tests to evaluate whether your liver or kidneys are working well. The tests will also check whether you have any electrolyte imbalances such as abnormal sodium or potassium levels. The tests will also measure the levels of your blood cells, which are responsible for fighting infection, carrying oxygen, and forming clots when you are bleeding. If you have had these blood tests done within the previous sixty days at MUSC, your medical record will be reviewed. If they were normal, you will not have to complete the blood tests.
- A urine sample will be collected at baseline and follow-up to determine if you are using any drugs including opioids.

- After staff has reviewed all the information collected, you will be contacted to inform you of your eligibility status. If you are eligible to enroll and choose to continue participation, you will be asked to come for weekly medication visits for 8 weeks. If you are not found eligible and/or do not choose to continue in the study, additional community resources can be made available to you upon request.

- If you are a woman of childbearing potential and/or a man capable of fathering a child, precautions should be taken throughout the course of the medication phase of the study. Examples of acceptable methods of birth control for participants involved in the study includes: birth control pills, patch, IUD, condom, sponge, diaphragm with spermicide, or avoiding sexual activity that could cause you to become pregnant. In addition, urine pregnancy tests will be completed at baseline visit. If you are pregnant, you will be withdrawn from the study.

2. Medication Visits (approximately 2-3 hours each in length):

- If you are eligible and decide to participate in the study, over the next 8 weeks you will come to the study center once per week to complete the medication visits. You will be encouraged to come well hydrated, but in a fasting state (i.e. not having eaten for 2 hours prior to the treatment visit). At these visits, you will complete questionnaires and urine testing much like the ones completed at the screening visit. These tasks will take about 30 minutes.

- You will complete a urine pregnancy test prior to each medication session (only if you are a woman of childbearing potential). The urine pregnancy test must be negative to participate.

- Each medication visit will include non-directive, supportive psychotherapy, which can include setting an intention for your session, supportive talk as needed throughout medication session, reflection on the experience of the session afterwards, and setting goals to work on after each session.

- Prior to being administered the medication, you will sit in a chair and be guided by the study doctor through a basic relaxation exercise. This exercise will help you to focus on your

breathing and is designed to help reduce any anxiety you may feel related to the medication sessions. The relaxation exercise will last about 10 minutes.

- After you complete the relaxation exercise, you will have your blood pressure and heart rate checked, and you will have a small, painless monitoring device placed on your finger which will measure the oxygen levels in your blood throughout the medication session.
- The study medication, ketamine, is given by intramuscular injection.
- After receiving the injection, you will be instructed to rest in a chair. After approximately 90 minutes, you will take complete several short questionnaires.
- Your blood pressure will be checked again, and if it is normal, the blood oxygen finger device will be removed, and the visit will be completed. If your blood pressure is high, you are feeling anxious, or you are not feeling like yourself, you will continue to be monitored by the study doctor until these symptoms return to normal.
- After completing the visit, you will be asked to have someone drive you home. If you do not have someone that can drive you home and live locally, transportation (such as a taxi) will be provided for you at no cost to you. If you live more than 20 miles from the study site and cannot arrange your own transportation you will not be able to participate in this study.

3. Follow-Up Visits (approximately 30 minutes each in length):
   - Completion of written questionnaires related to your mental and physical health. Questionnaires will also be related to recent use of alcohol and other drugs, your cravings for opioids, and your recent symptoms of depression and anxiety.
   - Follow-up visits can be completed either in person or virtually (via secure video software) depending on your preference.

C. DURATION

Participation in the study will take about 13 visits over a period of approximately 4 months. There will be an initial screening visit (approximately 2-3 hours), 8 study medication visits (approximately 2-3 hours each), and 4 follow-up visits (approximately 30 minutes).

D. RISKS AND DISCOMFORTS

There are risks involved with participating in this study, including risks associated with ketamine, study procedures, and loss of confidentiality.

Ketamine Risks:
Ketamine may cause some, all or none of the side-effects listed below. These effects are generally temporary and resolve within one hour, although they may last up to six hours. A study physician will monitor you until these symptoms resolve.

More Likely (10 percent to 50 percent):

- Perceptual changes (e.g. distortion of time and space, sense of illusions) and dissociation (including a sense of detachment or altered sense of reality)
- Feeling abnormal or drunk
- Elevated blood pressure
- Elevated heart rate
- Anxiety
- Sedation (sleepiness)
- Vertigo or dizziness
- Nausea
- Decreased pain threshold

Less Likely (5 percent to 10 percent):

- Injection site swelling, pain, redness, or discomfort

Rare (less than or equal to 5 percent):

- Bladder discomfort or increased frequency of urination (also called cystitis)
- Anaphylaxis

Unknown risks:

- High amounts of ketamine given to rats caused damage to different parts of the brain. It is not known whether this finding in rats will happen in humans. The amount of ketamine given to the rats was higher than what you will receive in this study.
- The added effect of repeated ketamine infusions is unknown. Chronic ketamine users (mostly ketamine abusers) may have structural and functional brain changes with associated memory problems. We are uncertain if this will occur at the frequency and duration proposed in this study.
- Bladder irritation and liver problems have been related to the repeated use of ketamine. We are uncertain if this will occur at the frequency and duration proposed in this study.
- The study treatment may also involve other risks, which are currently unforeseeable.
- If you become pregnant, the study treatment might involve risks to the embryo or fetus, which are currently unforeseeable.

Clonidine Risks:
If you experience clinically significant elevated blood pressure, you will be treated with a blood pressure medicaton called clonidine. Clonidine will be given by mouth. Most common clonidine side effects include dry mouth (40 percent), drowsiness (33 percent), dizziness (16 percent), constipation (10 percent) and sedation (10 percent). Syncope (or passing out) is a rare but possible side effect of clonidine."

Interviews and Surveys: The questions that will be asked may be sensitive in nature and may make you feel uncomfortable. You may be asked personal questions that you find distressing. You may refuse to answer any question(s) that you do not wish to answer.

Risks from Blood Draws: Risks associated with drawing blood from your arm include brief discomfort,

anxiety, and/or bruising. Infection, excess bleeding, clotting, or fainting is possible, although unlikely.

Electrocardiogram (ECG): The ECG procedure may cause some mild discomfort during the placement and removal of the leads to and from the skin. You may also experience some local irritation, redness, or burning in the areas where the leads are attached.

Risk of Loss of Confidentiality
There is a risk of a loss of confidentiality of your personal information because of participation in this study. Some answers you give during the research visits (like whether you use illegal drugs) may put you at risk if other people find out. To keep what you say private, your study records will use a code number instead of your name. We will protect your records to the extent allowed by law by keeping all your materials in locked file cabinets only accessible by research staff and all computer files will be secure password-protected files only accessed by research staff. Your research records are kept separate from your other medical records. Only research staff will have access to your private information.

Limits of Confidentiality:
Suspected or known abuse or neglect of a child, disabled or elder abuse, or threatened violence to self or others may be reported to appropriate authorities.

If you are or become pregnant and test positive for illegal drugs, it is a law that the South Carolina Department of Social Services (DSS) must be notified. You and your family will be evaluated by the agency. You could be ordered to mandatory drug treatment, lose custody of your children, or possibly be jailed.

Unknown Risks: The experimental treatments may have unknown side effects. The researchers will let you know if they learn anything during the study that might make you change your mind about participating in the study.

E. MEDICAL RECORDS AND/OR CERTIFICATE OF CONFIDENTIALITY

If you have a medical record at MUSC, it may be reviewed to determine your study eligibility. Results from blood and electrocardiogram testing that you may be asked to complete for the study will be included in your medical record. Other information about your study participation will not be in your medical record. This means that your research participation, drug and pregnancy testing, and responses to questionnaires will not be included in your MUSC medical record.

F. BENEFITS

If you receive ketamine, and it is more successful in treating your conditions compared to other antidepressants or types of psychotherapy, you may benefit from participating in the study. However, given the investigational nature of this study, benefit cannot be guaranteed or promised. Information gained from this study may help other investigators have a better understanding of the treatment of opioid use disorder and depression.

G. COSTS

There will be no cost to you because of participation in this study. If you choose to receive text message study reminders, normal data and usage rates will apply. You will be reimbursed for transportation costs (*ie,* via Uber, Lyft, or taxi) necessary for your participation in this study if you are unable to secure transportation to and from study visits otherwise and live within 20 miles from the study site. Reimbursement will equivalent to the amount you are charged by Uber, Lyft or a taxi company up to $100 for each trip to or from medication visits. If you live greater than 20 miles from the study site and cannot arrange your own transportation you will be unable to participate in this study.

H. PAYMENT TO PARTICIPANTS

Initial evaluation and eight weekly medication sessions will not result in compensation other than reimbursement for local travel expenses. If you choose to participate in follow-up assessments 1, 2, 4, and 8 weeks after your final medication session you will be paid $15 for each follow-up session completed. Payment for follow-up assessments and local travel expenses will be made using a pre-paid debit card, called a ClinCard. It works like a bank debit card and you may use the card to purchase goods or services everywhere Debit MasterCard is accepted. You will be given a ClinCard at the beginning of the study. Each time you receive payment for participation in this study, the money will be added to the card, as outlined in the payment schedule above. Details of the debit card system are explained on an additional sheet.

Payments that you receive from MUSC for participating in a research study are considered taxable income per IRS regulations. Payment types may include, but are not limited to: checks, cash, gift certificates/cards, personal property, and other items of value. If the total amount of payment you receive from MUSC reaches or exceeds $600.00 in a calendar year, you will be issued a Form 1099.

I. ALTERNATIVES

If you choose not to participate in this study, you could receive other treatments for your condition. The standard therapies for your opioid addiction include both medications (such as buprenorphine, methadone, and naltrexone) and counseling-based treatments (including group sessions such as Alcoholics Anonymous/Narcotics Anonymous and individual counseling sessions). There are many standard treatments for depression including medications and therapy (both group-based therapies and individual therapy or counseling). If you are currently taking any of these treatment options, you may continue any standard therapy.

<u>Withdrawal from the Study</u>

Your participation in this study is voluntary. You may refuse to take part in or stop taking part in this study at any time. You should talk with the investigator in charge of this study if you decide to do this. Your decision not to take part in the study will not affect your current or future medical care or any benefits to which you are entitled. The investigators and/or the sponsor may stop your participation in this study at any time if they decide it is in your best interest. They may also do this if you do not follow the investigator's instructions, or if the study is stopped by the study sponsor, the institutional review board (IRB), or by a regulatory agency (such as the FDA). If your participation is ended for medical reasons, you will be referred to a doctor or other health professional for care. You will be responsible for the cost of these services.

J. DATA SHARING

Information about you (including your identifiable private information and/or any identifiable biospecimens) may have all of your identifiers removed and used for future research studies or distributed to other researchers for future research without additional informed consent from you or your legally authorized representative.

K. DISCLOSURE OF RESULTS

Study data will not be shared with you to maintain confidentiality.

L. AUTHORIZATION TO USE AND DISCLOSE (RELEASE) MEDICAL INFORMATION

As part of this research study, your study doctor and his/her research team will keep records of your participation in this study.

The health information MUSC may use or disclose (release) for this research study includes information in your medical record, results of physical exams, medical history, lab tests or certain health information indicating or relating to your condition.

Your study doctor and his/her research team will use and disclose (release) your health information to conduct this study. The health information listed above may be used by and/or disclosed (released) to the following, as applicable:

- The sponsor of the study including its agents such as data repositories or contract research organizations monitoring the study;
- Other institutions and investigators participating in the study;
- Data Safety Monitoring Boards;
- Accrediting agencies;
- Clinical staff not involved in the study whom may become involved if it is relevant;
- Parents of minor children if less than 16 years old. Parents of children 16 years old or older require authorization from the child; or
- Health insurer or payer in order to secure payment for covered treatment;
- Federal and state agencies and MUSC committees having authority over the study such as:

    - The Institutional Review Board (IRB) overseeing this study; Committees with quality improvement responsibilities; Office of Human Research Protections; Food and Drug Administration; National Institutes of Health or Other governmental offices, such as a public health agency or as required by law.

Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them. You do not have to sign this consent form. If you

choose not to sign, it will not affect your treatment, payment or enrollment in any health plan or affect your eligibility for benefits. However, you will not be allowed to be a participant in this research study.

You will be given a copy of this consent form. Your authorization will expire at the conclusion of this study or, if you are participating in a study designed for the development of a drug or device, your authorization will remain in effect until the drug or device is approved by the FDA or until the company's application to study the drug/device is withdrawn. You have the right to withdraw your agreement at any time. You can do this by giving written notice to your study doctor. If you withdraw your agreement, you will not be allowed to continue participation in this research study. However, the information that has already been collected will still be used and released as described above. You have the right to review your health information that is created during your participation in this study. After the study is completed, you may request this information.

Your health information will be used or disclosed when required by law. Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury or disability and for conducting public health surveillance, investigations or interventions. No publication or public presentation about the research study will reveal your identity without another signed authorization from you.

If you have questions or concerns about this Authorization or your privacy rights, please contact MUSC's Privacy Officer at (843) 792-8740.

Regulations require that you be given a copy of the MUSC Notice of Privacy Practices (NPP) describing the practices of MUSC regarding your health information. One can be found at the end of this form.

M. SIGNIFICANT NEW FINDINGS

If there are significant new findings during the study, you will be notified.

N. STUDENT PARTICIPATION

Your participation or discontinuance will not constitute an element of your academic performance, nor will it be a part of your academic record at this Institution.

O. EMPLOYEE PARTICIPATION

Your participation or discontinuance will not constitute an element of your job performance or evaluation, nor will it be a part of your personnel record at this Institution.

P. CLINICALTRIALS.GOV

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Q. COLLECTION OF SPECIMENS

Blood and urine specimens may be collected in this study. Blood samples may be taken as part of the initial visit and will not be stored. Results of the blood test may be made a part of your MUSC medical record. Urine samples from females will be checked for pregnancy at the baseline visit and every medication visit. Results of urine testing will not be made a part of your medical record. These specimens will be used solely as part of this research study and will not be shared with other investigators or used for commercial profit. All specimens will be coded with your numeric study code to protect your confidentiality.

R. FUTURE CONTACT

The researcher in charge of this study might like to contact you in the future about other research opportunities. Please initial by your choice below for paper consents, or scroll down to the bottom of the screen and select your choice electronically:

____Yes, I agree to be contacted

____No, I do not agree to be contacted

You have the option of receiving appointment reminders and link to study surveys through text messages. Should you elect to receive text messages, normal cellular data usage and rates will apply. Please initial by your choice below for paper consents, or scroll down to the bottom of the screen and select your choice electronically:

____Yes, I agree to be contacted via text message

____No, I do not agree to be contacted via text message

Results of this research will be used for the purposes described in this study. This information may be published, but you will not be identified. Information that is obtained concerning this research that can be identified with you will remain confidential to the extent possible within State and Federal law. The sponsor and the Food and Drug Administration (FDA) will receive copies of the research records. The investigators associated with this study, employees of the sponsor, the FDA, and the MUSC Institutional Review Board for Human Research will have access to identifying information. All records in South Carolina are subject to subpoena by a court of law.

In the event of a study related injury, you should immediately go to the emergency room of the Medical University Hospital, or in case of an emergency go to the nearest hospital, and tell the physician on call

that you are in a research study. They will call your study doctor who will make arrangements for your treatment. If the study sponsor does not pay for your treatment, the Medical University Hospital and the physicians who render treatment to you will bill your insurance company. If your insurance company denies coverage or insurance is not available, you will be responsible for payment for all services rendered to you.

Your participation in this study is voluntary. You may refuse to take part in or stop taking part in this study at any time. You should call the investigator in charge of this study if you decide to do this. The data collected on you to this point remains part of the study database and may not be removed. Your decision not to take part in the study will not affect your current or future medical care or any benefits to which you are entitled.

The investigators and/or the sponsor may stop your participation in this study at any time if they decide it is in your best interest. They may also do this if you do not follow the investigator's instructions.

Volunteers Statement
I have been given a chance to ask questions about this research study. These questions have been answered to my satisfaction. If I have any more questions about my participation in this study or study related injury, I may contact the investigator in charge of the study at (843) 876-1193. I may contact the Medical University of SC Patient and Family Care Liaison (843) 792-5555 concerning medical treatment.

If I have any questions, problems, or concerns, desire further information or wish to offer input, I may contact the Medical University of SC Institutional Review Board for Human Research IRB Manager or the Office of Research Integrity Director at (843) 792-4148. This includes any questions about my rights as a research subject in this study.

I agree to participate in this study. I have been given a copy of this form for my own records. Please sign below.

_____
Signature of Participant Date

_____
Printed Name of Participant Date

_____

Signature of Person Obtaining Consent Date