NCT04592809

INFORMED CONSENT FORM

Title: Ketamine Versus Midazolam for Recurrence of Suicidality in Adolescents

IRB# STU-2020-0973
Date: April 20, 2025

Title of Study: Double-Blind Randomized Controlled Trial of Acute-Course of Ketamine Versus Midazolam for Recurrence of Suicidality in Adolescents

Consent of an Adult Participant
Consent and HIPAA Authorization to Be Part of a Research Study
To be conducted at
The University of Texas Southwestern Medical Center
Children's Medical Center of Dallas and any of its affiliated entities
John Peter Smith Health Network (JPS)

Version 6.8
02-26-2025

Key Information about this Study

Please read this consent form carefully and take your time deciding whether you would like to be part of this research study. Please ask the study team to explain any words or information that you do not understand. If you decide to be a part of this study, you will be given a copy of this form to keep.

The goal of this research study is to identify early signs that ketamine is safe and effective in lowering the chance of future suicide acts in youths who are at risk for future suicide attempts. This study will also try to find out if ketamine can lower thoughts of ending your life in as short as hours or days, compared to weeks.

You will get either ketamine or midazolam four times during the first two weeks of study participation. Both of these medications will be given through an IV, a tube that will be placed in a vein of your arm. In this study, midazolam will serve as an active placebo drug, which means it mimics the side effects of the study drug (ketamine). Midazolam will be referred to as "placebo" in this consent form. You must also be receiving standard of care from your mental health providers.

You will be asked to meet with the study team for approximately 16 visits (including today). Sometimes you may be able to meet with the study team by phone or video without having to come in person. When you are here in person, that may affect your ability to attend school or work.

You will also be asked to not take some medications while you are taking part in the study. This is to make sure that you do not take any medications that will affect the study drug. Some medications may be stopped completely, while others may be stopped right before the study drug visit. Your study doctor will review all your medications with you and will let you know if your medications need to be stopped. Some examples of these medications that you cannot take include:

- Medications for recreational purposes;
- Medications for Attention-deficit/hyperactivity disorder (ADHD) within 24 hours of the study drug administration. The study team will not ask you to discontinue any treatment (except for not taking ADHD medications for 24 hours before study drug administration) just for the sake of taking part in this study;
- Other medications that may affect the study drug.

Taking part in this research study may have risks. One risk is that you may have side effects with study drug administration. The most common side effects with ketamine are feeling sleepy, feeling dizzy, blurring of vision, difficulty with your balance, feeling unusual, headache, nausea, diarrhea, anxiety, and stomach pain. The most common side effects with midazolam are hiccups, nausea, vomiting, coughing, headache, and feeling sleepy. However, the study doctors do not know all the side effects that may happen and will always monitor you during the study.

Information about this form

You may be a good fit for this research study. You will be provided 2 forms as part of the Informed Consent process. This form, Part 1, and a secondary form, Part 2, will be provided to you to keep. Part 1 of the consent reviews study

details in full. Part 2 describes local site information. Please review both forms in detail prior to agreeing to participate in this study.

Please take time to review this form carefully. You should talk to the study team about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or a doctor) about taking part in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

Please tell the study team if you are taking part in another research study.

Voluntary Participation - You do not have to participate if you do not want to. You may also leave the study at any time. If you decide to stop taking part in this research study, it will not affect your relationship with the staff or doctors at your local institution. Whether you participate or not will have no effect on your legal rights or the quality of your health care.

General Information – "Who is conducting this research?"

Principal Investigator
The Principal Investigator (PI) is the person who directs this study; the PI is responsible for protecting your rights, safety, and welfare as a participant in the research. The PI for this study is Madhukar H. Trivedi, M.D., with the Department of Psychiatry at UT Southwestern Medical Center. You may contact the UTSW study staff directly at 682-376-8619 or contact our UTSW research clinic at 214-648-4689.

Funding
The National Institute of Mental Health (NIMH), a federal agency that promotes scientific research, is funding this study. NIMH is providing money to UT Southwestern so that the PI and study team can conduct the study.

Purpose – "Why is this study being done?"

The goal of this study is to identify early signs that ketamine is safe and effective in lowering the chance of future suicidal acts in youths who are at risk for future suicide attempts. This study will also try to find out if ketamine can lower thoughts of ending your life in as short as hours or days, compared to weeks.

You are being asked to participate in this research study based on the information we collected over the phone. This study is being done because of limited treatment options for youth who have recently tried to harm themselves. In fact, there are no medications shown to be useful in preventing future thoughts or acts of harming themselves in youths who have recently tried to harm themselves. Our current standard for such youths is to try medication and/or therapy for depression and may include a stay at a hospital or intensive outpatient program (IOP).

If you qualify for this study, you will be randomly (like a flip of a coin) assigned to one of 2 study drugs, either ketamine or midazolam. Midazolam in this study will serve as an active placebo study drug, which means there is not likely to be a benefit from this medication for reducing suicidal thoughts. Both of these medications will be given through a tube that will be placed in a vein of your arm. You will have the study drug on 4 separate days over the first two weeks of study participation. During this study, you **must** also continue to take treatments (medication and/or therapy) through your regular treatment provider(s) and may be enrolled in an inpatient or IOP treatment program.

Investigational Use of a Drug
This study involves the use of ketamine, a drug that has not yet been approved by the U.S. Food & Drug Administration (FDA) for treating suicidal behaviors.

This study will help find out what effects, good and/or bad, this drug may have on people who take it and its effect on

suicidal thoughts and acts of self-harm with the intention to die. The safety of this drug in humans has been tested in prior research studies; however, some side effects may not yet be known.

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

Information about Study Participants – "Who is participating in this research?"

You are being asked to be a participant in this study because you are between the ages of 13-18 and within the past 90 days had an increase in suicidal thoughts and acts of self-harm with the intention to die.

How many people are expected to take part in this study?
This study will enroll approximately 114 study participants between the ages of 13-18.

Information about Study Procedures – "What will be done if you decide to be in the research?"

While you are taking part in this study, you will be asked to attend 16 visits over a period of approximately 12-14 weeks (including today). Visits include a Screening Visit, 4 Study Drug Visits, and 11 Follow-Up Visits (combination of in-person and remote visits).

Research staff, possibly from other study sites, may observe study procedures being performed for training purposes.

Screening – After you sign this consent to participate, exams, tests, and/or procedures may be done as described in the following sections to find out if you can continue in the study; this is called screening. We may be able to use the results of exams, tests, and/or procedures you completed before enrolling in this study. You will be told which results we will use, and which procedures will not be repeated. Many of the procedures are described below as "**standard care**" and would be done even if you do not take part in this research study. You will be told which procedures are for "**research only**".

Screening Visit (4 hours):

- *Physical examination:* We will measure your height, weight, temperature, oxygen saturation, pulse, and blood pressure, listen to your heart and lungs, as well as collect your medical history. The physical exam will not include a pelvic, rectal, or breast exam.
- *Pregnancy Test:* If you are capable of becoming pregnant, a urine pregnancy test will be done as a safety measure. If your pregnancy result is positive, you will not be eligible to be a part of this study. Results of the test will be shared with you.
- *Self-report questionnaires*: You will be given electronic questionnaires to answer questions about how you are feeling. These questions will give us information about how you are doing in the study, so it is important to complete these questions as we instruct you.
    - If you do not feel comfortable answering a question, you will not be required to answer it, but you must let the study team know.
- *Assessor Interviews*: You will be interviewed to assess your depressive symptoms, mood, feelings and eligibility for this study. If available and you agree, we may also ask your parent/LAR/guardian about your symptoms.
- *Electrocardiogram* (ECG): Sticky patches that are connected to a machine that shows the electrical activity of your heart, are placed on your chest. Hot and cold drinks and food should be avoided 30 minutes before an ECG measurement whenever possible.
- *Resting Electroencephalogram (EEG):* This is an optional procedure. An elastic cap containing electrodes will be placed on your scalp. The electrodes will measure the electrical activity of your brain while at rest for 10min.
- *Urine Sample*: Your urine will be collected to test for a wide range of disorders, as well as possible drug use.

Results of the test will be shared with you.

- *Review of medications:* We will talk with you about any medicines that you take.
- *Review of Medical and Psychiatric history:* We will talk with you about your medical and psychiatric history.
- *Blood Sample:* Blood (about 5 teaspoons) will be taken from a vein in your arm for safety tests (e.g., complete blood count, and basic metabolic panel). Optionally, blood (about 3.5 tablespoons) may also be taken for biobanking (repository for storing biological samples for use in research).

The results of these exams, tests, and/or procedures will be reviewed to assess whether you will be allowed to continue in the study. If you are not allowed to continue in the study, the study team will discuss the reasons with you, and will discuss other possible options.

Randomization
If eligible to continue in the study, you will be randomly (like a flip of a coin) assigned to one of 2 study drugs, either ketamine or midazolam. This is explained below.

Assignment to Study Groups
When it is determined that you are eligible for the study, you will be assigned 1:1 by chance (like flipping a coin) to one of 2 study groups. You will get either ketamine or midazolam four times during the first two weeks of study participation. Study medication will be prepared by pharmacy staff. Neither you nor the study team will know whether you are receiving ketamine or midazolam. In the event of an emergency, there is a way for the researcher to find out which study drug you are receiving.

Study Drug Visits:
Infusion visits will occur on Days 0, 3, 7, and 10 (plus or minus 1 day to allow for holidays, weekends, and missed visits). Each participant will be allowed to rest in a semi-recumbent position (that is, elevation of your head to the bed would be between 30-45º). A qualified study team member or treating anesthesiologist (doctor who specializes in the administration of anesthetics) will place a tube in a vein of either of your arms. Pulse, blood pressure, and digital pulse-oximetry will be monitored. Oxygen by face mask or nasal cannula will be administered as needed. Vital signs monitoring will be recorded beginning five minutes prior to receiving the study drug.

ECG monitoring may be used during infusion. An anesthesiologist or a medical professional will be present throughout the infusion, and a medical cart will be available for emergencies. After the infusion, you will be given a snack and allowed to rest. Two hours after the end of the study drug infusion, the study physician will evaluate you for discharge readiness. If stable, you will be discharged home in care of a responsible adult. Subsequent study drug visits will resemble the first study drug administration visit.

Day 0: Initial Study Drug Visit (4-5 hours):

- *Fasting:* You will arrive to your appointment fasting. Fasting means no food or liquids for 6 hours (light meals) or 8 hours (regular meals) before your appointment. You will be able to drink clear liquids up to 2 hours before the infusion. We will provide you with a one-page summary of what you can consume before the infusion.
- *Physical examination:* We will measure your height, weight, temperature, oxygen saturation, pulse, and blood pressure, listen to your heart and lungs, as well as collect your medical history. The physical exam will not include a pelvic, rectal, or breast exam
- *Computer testing:* You will complete a cognitive assessment via computer or tablet which will assess the process of gaining knowledge and understanding.
- *Self-report questionnaires*: You will be given electronic questionnaires to answer questions about how you are feeling. These questions will give us important information about how you are doing in the study, so it is important to complete these questions as we instruct you.
    - If you do not feel comfortable answering a question, you will not be required to answer it, but you must let the study team know.

- *Assessor Interviews*: We will interview you to assess your depressive symptoms, mood, and feelings. If available and you agree, we may also ask your parent/LAR/guardian about your symptoms.
- *Pregnancy Test:* If you can become pregnant, a pregnancy test will also be done before you receive the study drug. If your pregnancy test results are positive, you will not be able to receive the study drug. Results of the test will be shared with you.
- *Urine Sample*: Your urine will be collected to test for a wide range of disorders, and if applicable possible drug use. Results of the test will be shared with you.
- *Review of medications:* We will talk with you about any new medicines you are taking.
- *Review of Side Effects*: We will ask you questions about any side effects since signing the consent form.
- *Study Drug:* If eligible to continue in the study, you will receive your first study drug dose.
- *Observation:* We will observe you after the end of the study drug administration for at least two hours.
- *Vital Signs:* We will take your blood pressure, heart rate, pulse, and oxygen saturation many times during your visit.
- *Discharge:* You will be given a snack and assessed by a study doctor before being released into the care of a responsible adult to pick you up. <u>You must agree not to drive or operate heavy machinery within 24 hours of study drug administration.</u>

Days 3, 7 and 10 (4-5 hours):

- *Fasting:* You will arrive to your appointment fasting. Fasting means no food or liquids for 6 hours (light meals) or 8 hours (regular meals) before your appointment. You will be able to drink clear liquids up to 2 hours before the infusion. We will provide you with a one-page summary of what you can consume before the infusion.
- *Physical examination:* We will measure your height, weight, temperature, oxygen saturation, pulse, and blood pressure, listen to your heart and lungs, as well as collect your medical history. The physical exam will not include a pelvic, rectal, or breast exam
- *Self-report questionnaires*: You will be given electronic questionnaires to answer questions about how you are feeling. These questions will give us important information about how you are doing in the study, so it is important to complete these questions as we instruct you.
    - If you do not feel comfortable answering a question, you will not be required to answer it, but you must let the study team know.
- *Assessor Interviews*: We will interview you to assess your depressive symptoms, mood, and feelings. If available and you agree, we may also ask your parent/LAR/guardian about your symptoms.
- *Review of medications:* We will talk with you about any new medicines you are taking.
- *Review of Side Effects*: We will ask you questions about any side effects since your last visit.
- *Urine Sample*: Your urine will be collected to test for a wide range of disorders, and if applicable, possible drug use. Results of the test will be shared with you.
- *Pregnancy Test:* If you are capable of becoming pregnant, a pregnancy test will also be done before you receive the study drug. If your pregnancy test results are positive, you will not be able to receive the study drug. Results of the test will be shared with you.
- *Study Drug:* If eligible to continue in the study, you will receive your next study drug dose. You will receive your final study drug on Day 10.
- *Observation:* We will observe you after the end of the study drug administration for at least of two hours.
- *Vital Signs:* We will take your blood pressure, heart rate, pulse, and oxygen saturation several times during your visits.
- *Discharge:* You will be given a snack and assessed by a study doctor before being released into the care of a responsible adult to pick you up. <u>You must agree not to drive or operate heavy machinery within 24 hours of study drug administration.</u>

Day 14 (2 hours):

- *Self-report questionnaires*: You will be given electronic questionnaires to answer questions about how you are feeling. These questions will give us important information about how you are doing in the study, so it is important to complete these questions as we instruct you.
    - If you do not feel comfortable answering a question, you will not be required to answer it, but you must let the study team know.
- *Assessor Interviews*: We will interview you to assess your depressive symptoms, mood, and feelings. If available and you agree, we may also ask your parent/LAR/guardian about your symptoms.
- *Review of medications:* We will talk with you about any new medicines you are taking.
- *Review of Side Effects*: We will ask you questions about any side effects since your last visit.
- *Physical examination:* We will measure your height, weight, temperature, oxygen saturation, pulse, and blood pressure, listen to your heart and lungs, as well as collect your medical history. The physical exam will not include a pelvic, rectal, or breast exam.
- *Urine Sample*: Your urine will be collected to test for a wide range of disorders, and if applicable, possible drug use. Results of the test will be shared with you.
- *Computer testing:* You will complete a cognitive assessment via computer or tablet, which will assess the process of gaining knowledge and understanding.
- *Vital Signs:* We will take your blood pressure, heart rate, pulse, and oxygen saturation during your visit.
- *Resting Electroencephalogram (EEG):* This is an optional procedure. An elastic cap containing electrodes will be placed on your scalp. The electrodes will measure the electrical activity of your brain while at rest for 10min.
- *Blood Sample:* Blood (about 5 teaspoons) will be taken from a vein in your arm for safety tests (e.g., complete blood count, and basic metabolic panel). Optionally, blood (about 3.5 tablespoons) may also be taken for biobanking (repository for storing biological samples for use in research).

Days 21-77 (30-45min):

Following study drug administration visits, you will continue to be monitored by study staff. These visits will be either in clinic or remote based on your preference.

- *Self-report questionnaires*: You will be given electronic questionnaires about how you are feeling. These questions will give us important information about how you are doing in the study, so it is important to complete these questions as we instruct you.
    - If you do not feel comfortable answering a question, you will not be required to answer it, but you must let the study team member know.
    - If remote, a member of the study team will email you a link to complete the questionnaires. You will have 7 days to complete these questionnaires.
- *Assessor Interviews*: We will interview you to assess your depressive symptoms, mood, and feelings. If available and you agree, we may also ask your parent/LAR/guardian about your symptoms.
- *Review of medications:* We will talk with you about any new medicines you are taking.
- *Review of Side Effects*: We will ask you questions about any side effects since your last visit.

Day 84 (2 hours):

This is the final study visit and will be in person.

- *Self-report questionnaires*: You will be given electronic questionnaires to answer questions about how you are feeling. These questions will give us important information about how you are doing in the study, so it is important to complete these questions as we instruct you.
    - If you do not feel comfortable answering a question, you will not be required to answer it, but you must let the study team know.
- *Assessor Interviews*: We will interview you to assess your depressive symptoms, mood, and feelings. If available and you agree, we may also ask your parent/LAR/guardian about your symptoms.
- *Review of medications:* We will talk with you about any new medicines you are taking.

- *Review of Side Effects*: We will ask you questions about any side effects that arose since your last visit.
- *Urine Sample*: Your urine will be collected to test for a wide range of disorders, and if applicable, possible drug use. Results of the test will be shared with you.
- *Physical examination:* We will measure your height, weight, temperature, oxygen saturation, pulse, and blood pressure, listen to your heart and lungs, as well as collect your medical history. The physical exam will not include a pelvic, rectal, or breast exam.
- *Computer testing:* You will complete a cognitive assessment via computer or tablet which will assess the process of gaining knowledge and understanding.
- *Resting Electroencephalogram (EEG):* This is an optional procedure. An elastic cap containing electrodes will be placed on your scalp. The electrodes will measure the electrical activity of your brain while at rest for 10min.
- *Blood Sample:* This is an optional procedure. Blood (about 3.5 tablespoons) will be taken from a vein in your arm for biobanking (repository for storing biological samples for use in research).

Samples collected for scientific/genetic research
Blood samples will be collected and processed for safety assessment and optionally for biobanking in a USTW repository (IMPACT). If you agree to provide your blood for biobanking, your de-identified blood samples will be used for future research. You will be informed if testing on your samples for this study will change.

If you agree to provide your blood for biobanking, different substances in your blood samples may be tested. Your de-identified blood samples may also be used for genetic research. Genetic research is the study of Deoxyribonucleic Acid (DNA). DNA carries information that determines our features, such as, the color of our hair and eyes. DNA may also explain why some people respond to some medications and others do not. It may also explain why some people get some diseases and others do not. We do not plan to release genetic information to you. We also do not plan to release your genetic information to others where they can identify you. However, there are risks in case your information is released by mistake. The measures being taken to protect your privacy are discussed below (in section: "**Risk associated with genetic information**") and make this possibility unlikely.

In addition, the results of tests done on these samples are only for research. They will not be used for your medical care. They will not be used to make a diagnosis about your health. Therefore, these results will not be given to you or the study doctor/staff.

If you agree to provide your blood for biobanking, some portion may be frozen or stored indefinitely for this future use. The researchers will keep this sample until it is finished, becomes unusable, or until the study team decide to discard the sample. Stored de-identified specimens may be analyzed in the future using additional technologies without you being asked to sign another consent form. If you wish to withdraw your sample from the biobank, written request must be sent to the Principal Investigator (see section: Withdrawing your research data from the repository)

Could your participation end early?
There are several reasons why the study team may need to end your participation in the study (early withdrawal). Some reasons are:
- The study team believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- You do not follow instructions from the study team.
- The study is stopped for lack of funding, or safety concerns.

You may have a relapse of symptoms and may experience suicidal thoughts or behaviors. The study doctor will work with your clinical provider to ensure adequate treatment, which may include hospitalization. You will continue to receive assessments throughout the 12-week study period. If you are hospitalized or enter a treatment facility during the study,

we will attempt to complete the research assessments remotely (via telephone for clinician rated and electronically for self-report) if feasible and will resume upon your discharge.

The study team will talk with you about your options for medical care when your participation in this study ends.
It is possible that this study will identify information about you that was previously not known, such as abnormal lab results. Any clinically relevant results will be told to you. Clinically relevant means that the information shows that you may have abnormal lab values. In that case, we will try to let you know using the contact information you gave to the study team.

Withdrawing your research data from the repository
If your participation in this study ends early, we will keep the data that we already collected. If you wish to withdraw all of your research data, you may do so by sending a request in writing to:

Attn: Dr. Madhukar H. Trivedi, MD
UT Southwestern Medical Center
Department of Psychiatry
1440 Empire Central Drive
Level 3 Mood Disorders
Dallas, TX 75247-9119

How will my information be used?
By agreeing to participate in this study, your de-identified information could be used for future research studies or sent to other investigators for future research studies without additional consent. These future research studies will be reviewed by an oversight group known as an Institutional Review Board if required by law. The information that identifies you will be removed. If you do not want your de-identified information to be used for future research studies without your consent, you should not participate in this study.

Risks – "What are the risks of participation in the research?"

The following section will explain the risks related to being part in this research study. You should talk to your study doctor about any side effects or other problems that you have while in the study.

For more information about risks, ask the study team. We will tell you about any important new findings which appear during this research study which may relate to your willingness to continue taking part.

Risks from the research: The Principal Investigator has designed this study to learn how well the study drug compares to commonly accepted treatment(s). There is a risk that the effectiveness and/or safety of the study drug may not be as good as the most commonly accepted treatments. You may get a study drug that does not help treat your symptoms or that makes your symptoms worse.

Risks from the specific study drug: Side effects from this study will usually go away soon after you stop taking the study drug. In some cases, side effects can be long lasting or may never go away.

Everyone taking part in the study will be watched carefully for any side effects. However, the study doctors do not know all the side effects that may happen. Be sure to tell your study doctor right away, about any side effect that you have while taking part in the study.

Side effects can range from mild to serious. Serious side effects are those that may require hospitalization, are life threatening or could cause death. The frequency that people experience a certain side effect can range from many

(likely), few (less likely) or only one or two (rarely). There may be unexpected side effects that could be life threatening or could cause death.

The research team will tell you about any important new findings which develop during the study which may relate to your willingness to continue taking part.

Risks from Assessments/Interview: While we have made every effort to reduce burden, the initial visit, which includes a research interview (approximately 4 hours), may upset you. Follow-up visits are much shorter, (30-60 minutes to complete). If child abuse is detected at any point during the study, the study team is required to follow mandatory state reporting laws.

Risks from Ketamine/Midazolam:
Ketamine is generally well tolerated. The most common risks are feeling sleepy, feeling dizzy, blurring of vision, difficulty with your balance, feeling unusual, headache, nausea, diarrhea, anxiety, and stomach pain. In addition, while less common, ketamine has been associated with transient neuropsychiatric risks, including dissociative symptoms, such as hallucinations, delusions, incoherent and/or incomprehensible speech, memory loss or amnesia. Another possible side effect of ketamine is ketamine-induced cystitis, which is inflammation of the bladder. 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. In addition, the added effect of repeated ketamine infusions is unknown. Chronic ketamine users (mostly ketamine abusers) have structural and functional brain changes with associated cognitive problems. We are uncertain if this will occur at the frequency and duration proposed in this study.

The most common risks reported with midazolam are hiccups, nausea, vomiting, coughing, headache, and feeling sleepy. Higher doses of midazolam may lead to more serious cardiorespiratory risks, although the doses in the study are much lower, and not expected to lead to serious risks. We will monitor you continuously for any side effects and begin appropriate treatment if necessary.

Ketamine and midazolam are both associated with the risks of misuse, abuse, and addiction and the development of physical dependence. When taken on a regular basis, suddenly stopping either ketamine or midazolam may be associated with symptoms of withdrawal such as excessive anxiety, shaking, and sweating. The use of ketamine or midazolam as planned in this study (twice a week for two weeks) has not been associated with symptoms of withdrawal.

Risks from Blood Draw and IV Site Tenderness: The risks involved in drawing blood from a vein may include, but are not limited to, momentary discomfort at the site of the blood draw, possible bruising, redness, and swelling around the site, bleeding at the site, feeling of lightheadedness when the blood is drawn, and rarely, an infection at the site of the blood draw. Site tenderness may include pain during the injection, and tenderness, redness or swelling.

Risks from Electroencephalogram (EEG): The risks include discomfort from wearing a close-fitting elastic cap and the use of an electrolyte solution.

Risks from Electrocardiogram (ECG): There is generally no risk with having an ECG. The sticky patches may pull your skin, cause redness, or itching.

Risks of Suicidal Behavior: As you will have current suicidal ideation or have made a recent suicide attempt, ongoing suicidal ideation and behaviors is a risk throughout the study period. We will provide referral information to you. If at any point during the study we think that you are a possible suicidal risk and you are not willing to address this issue, then we will contact emergency mental health services to initiate an evaluation or inpatient care. We will regularly assess you for suicidal risk, the ability to adhere to a safety plan, and confer with the PI as to whether or not you are safe to continue at the current level of care, and you will be encouraged to contact your clinical care provider for

additional treatment options.

If during the study, the study team believes you are a risk to yourself or others, and have increased suicidal ideation and/or behavior, we will contact your primary mental health provider (psychiatrist, therapist or pediatrician) indicated on the Release of Information (ROI) that will be collected at screening.

Risks of Unimproved or Worsening of Psychiatric Illness: Continued or worsening of underlying psychiatric illness (such as depression and anxiety) is always a risk, even for those treated with medication and/or therapy. Similarly, there are risks associated with specific treatments for these disorders, including risks of development of mania or behavioral activation, worsening of suicidal thoughts, etc. that are associated with antidepressant treatment. While these treatments are not specific to the study drug, it is important for the study team, you, and your family to be aware of the potential risks connected not only with the underlying illness, but with these treatments, as well.

Risks of Oxygen Use: Oxygen by face mask or nasal cannula will be administered as needed. You may experience claustrophobia or discomfort while wearing the oxygen mask or nasal cannula.

Risk of Loss of Confidentiality: The potential for a breach in confidentiality always exists, specifically with written research data and study data. Study plans have been designed to protect your privacy and confidentiality. Throughout the study, all data, including that collected during the recruitment phase, will only be identified by a unique identification number and subject code using letters and numbers. The data that identifies you will be blinded in all data analyses. Only authorized staff will have access to patient information. All study information that identifies you will be stored separately from the study data and will be stored in a locked cabinet.

Risks to Sperm, Embryo, Fetus or Breast-fed Infant: The effects of the study drug on fertility, the human embryo, the fetus, or the breast-fed infant are unknown.

Females: Taking part in the study might harm your unborn child or breastfed baby. You cannot take part in this study if you are pregnant or breastfeeding a child. You must agree not to become pregnant while you are in this study, and for 6 weeks after your last study drug administration.

If you are sexually active and able to get pregnant you must use a highly effective method of birth control during the study and for 6 weeks after your last study drug visit.

Examples of highly effective birth control methods that can be used while in this study include:

- Hormonal contraceptives (like “the pill”)
- Contraceptive injections
- Intrauterine devices (IUD)
- Contraceptive patches
- Double barrier methods
- Male partner sterilization
- Abstinence (avoiding sexual intercourse)

The study doctor may share this information with NIMH (the Study Sponsor) and the Institutional Review Board/ Ethics Committee that monitors this trial.

If you are sexually active, the type of birth control you use must be discussed with the study doctor before you begin the study. The study doctor must approve the method you use before you can enter the study.

If you become pregnant during the study, you must tell the study doctor immediately. You will have to stop taking the study drug. The study doctor will advise you about your medical care and will ask you to allow him/her to collect information about your pregnancy and the health of your baby.

Males: The effect of the study drug on your sperm is unknown.

If you are sexually active with a young female of childbearing potential, you and your partner must use a highly effective method of contraception (see list above) from when you start taking the study drug until 3 months after your last study drug visit. This is done to prevent pregnancy.

Other considerations for male participants regarding sexual activity:

- You must not donate sperm during the study and for 3 months after your last dose of study drug;
- If you had a vasectomy, you do not need to use a condom for birth control
- If your partner becomes pregnant from the time of the first drug administration until 3 months after your last drug administration, you must tell the study doctor immediately. We may ask you and your partner to allow us to collect information about her pregnancy and the health of the baby.

Risk associated with genetic information: We do not plan to release genetic information to you. We also do not plan to release your genetic information to others where they can identify you. However, there are risks in case your information is released by mistake. The measures being taken to protect your privacy are discussed below and make this possibility unlikely.

Releasing genetic information to you could cause psychological distress, anxiety, or family problems. Releasing this information to others, such as including it in your medical record, may pose a possible risk of discrimination, or increase difficulty in obtaining or maintaining disability, long-term care, or life insurance.

Even though the results of genetic testing may not be linked to you, it is possible that people of your ethnic background may be found to be at more risk for certain diseases based on future genetic treatment and this information might harm you in the future as a member of the group. Also, there may be unknown risks of genetic testing in the future.

Retention of Samples for Future Research

Some or all of your de-identified blood samples will be stored forever until the blood sample runs out or it is destroyed. This will allow for future research to be done as new discoveries are made. The sponsor and study team will ensure that your blood samples are kept safe. You can withdraw your consent for your blood samples to be used for future research. In this case your blood samples will be destroyed only after they are no longer needed for this study. You will need to tell the study team that you are withdrawing your consent for your blood samples to be used for future research. This will not affect your access to the care, medicine, and equipment you would otherwise be getting. This can be done at any time and for any reason.

As technology advances, there may be new ways to access and trace information back to you (or your close biological relatives) that we cannot predict. The study team will use reasonable measures within its control to protect your information. Even though no one would be able to know just from looking at your genetic data that the information belongs to you, there is a potential risk to you and to your family. This is because your genetic information is unique to you. Therefore, there is a chance that someone could trace the information back to you or your close biological relatives. This could happen if you (or your biological relatives) had DNA testing done another time that could be matched against your results from this study. The risk of this happening is small but could grow in the future.

The study team may use any of your blood samples from this study for research that helps us understand:

- How ketamine may work, or why it/they may cause side effects
- Depression, suicidal thoughts/behaviors, and other neuropsychiatric/neurodegenerative disorders
- How to identify which people may respond differently to ketamine

- Why people may respond differently to placebo

To protect your privacy, your blood samples will be labeled with your study number and participant number. No personal identifiers are used (such as name, initials, social security number). The scientists doing the research will not know your identity.

Your de-identified blood samples may be sent to other members of UT Southwestern Medical Center and the Center for Depression Research and Clinical Care.

Your de-identified blood samples may also be shared with research partners for research purposes. Your blood samples will not be sold, loaned or given to any other independent groups for their own use. Research partners working with the investigators are not allowed to share blood samples with anyone who is not authorized by the sponsor, investigators, or UT Southwestern Medical Center. The investigators will manage what is done with your samples.

Other than the payments for study visits described in this consent, you will not be paid for any use of your samples, results, or inventions made from research on them. You are providing your samples for use by the investigators. The investigators (and research partners, where applicable) plan to own the use of the results, treatments, or inventions that can be made from this research.

Protections for Genetic Information

A Federal law, called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

Can I stop participating in this study?

If you decide to withdraw from this study early, please talk about your decision with the principal investigator. You are free to withdraw from the study at any time. You will need to have follow-up procedures to safely withdraw. The study physician will work with your clinical provider to ensure information on adequate alternate treatment is provided. You will be encouraged to continue with the follow-up assessments even if you have withdrawn from treatment or intensive outpatient program (IOP). However, if you choose to withdraw from all aspects of the study, you will be asked to return for a final assessment.

What happens if I stop the study early?

If you stop the study early, the study team will ask you to come for a final follow-up visit. This is to make sure that you are in good health. This information will be added to your study record.

If you have side effects after you stop the study early, the study team may contact your doctors who you see regularly. By signing this consent form, you agree that this information can be obtained and added to your study record unless you indicate otherwise.

If you stop the study early and withdraw your consent at any time, you agree not to limit the use of your study information collected up to the point of the end of study visit. The study team will not collect any new information from you for any parts of the study from which you have withdrawn. Your collected samples will continue to be analyzed as described in this form unless you specifically ask for your samples to be destroyed. This is to protect the quality of the study.

Are there risks if you also participate in other research studies?
Being in more than one research study at the same time may increase your risks. It may also affect the results of the studies. You should not take part in more than one study without approval from the study team.

Benefits – "How could you or others benefit from your taking part in this study?"

The benefits of being part of this study include having a careful assessment of your suicidal risk for twelve weeks. The principal investigator will be on call to help the study team deal with any potential clinical emergencies that emerge either during the relatively brief study drug administration or during follow-up assessments. You may experience improvement in suicidality and/or your underlying psychiatric illness, regardless of study drug (i.e., ketamine or midazolam). In addition, you may feel a sense of accomplishment from being part of this study and research and contributing to the knowledge of treatment for youth with suicide attempts and suicidal ideation.

There is no guarantee or promise that you will receive any benefit from this study, regardless of whether you receive ketamine or midazolam.

We hope the information learned from this study will benefit other people with similar conditions in the future.

Alternative procedures or course of treatment – "What other options are there to participation in this study?"

Instead of taking part in this study, you may choose other alternative treatments. The study doctor will discuss and tell you about available alternative treatment options.

Payments – "Will there be any payments for participation?"

You will be paid at a rate of $100 for the four study drug visits, $75 for longer assessment days (days 14 and 84) and $25 for all other follow-up visits. A total of $775.00 may be paid to you for your participation and will be based on the visits you attend. In certain circumstances, assistance with transportation may be provided.

Costs – "Will taking part in this study cost anything?"

You or your health insurance company will be responsible for the cost of treatments and procedures that would be done whether or not you took part in this study, such as hospitalization, ER visits, IOP, outpatient care, and any routine medical care associated with those.

All procedures listed above under "Information about Study Procedures" will be covered by the Study Team. Ask the study team if you have any questions about what it will cost you to take part in this study (for example bills, fees, or other costs related to the research).

NIMH, the sponsor will provide the study drug free of charge during this study.

Confidentiality and HIPAA Authorization – "How will your records be kept confidential?"

Information we learn about you in this study will be handled in a confidential manner, within the limits of the law. It is important to know that if we learn of possible abusive behavior, we must follow local and state reporting laws. In addition, under Texas Privacy Laws, unless an exception applies (e.g., adolescent would be in danger), the study team is required to disclose results of pregnancy and drug screen testing to the parent/guardian. In the event that we believe that you are in danger of hurting yourself or someone else, we will disclose this information to ensure safety.

If we publish the results of the study in a scientific journal or book, we will not identify you. The Institutional Review Board and other groups that have the responsibility of keeping track of research may want to see study data which identify you as a participant in this study.

Your personally identifiable information collected during this study will not be used or distributed for future research studies; however, your de-identified information could be used for future research studies or sent to other investigators for future research studies without additional consent. The information that identifies you will be removed. If you do not want your information to be used for future research studies without your consent, you should not be part of this study.

Certificate of Confidentiality:
This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate **CANNOT BE USED** to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate **DOES NOT** stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also **DOES NOT** prevent your information from being used for other research if allowed by federal regulations.

The study team may release information about you when you say it is okay. For example, you may allow the study team to give information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

With this Certificate of Confidentiality, the researchers cannot be forced to disclose information that may identify you in any judicial, administrative, legislative, or other proceeding, whether at the federal, state, or local level. There are situations, however, where we will voluntarily disclose information consistent with state or other laws, such as:

- to United State Department of Health and Human Services (DHHS) for audit or program evaluation purposes;
- information regarding test results for certain communicable diseases to the Texas Department of State Health Services, including, but not limited to HIV, Hepatitis, Anthrax, and Smallpox;
- if you pose imminent physical harm to yourself or others;
- if you pose immediate mental or emotional injury to yourself;
- if the study team learns that a child has been, or may be, abused or neglected; or
  if the study team learns that an elderly or disabled person has been, or is being, abused, neglected or exploited.

How will my information and/or tissue samples be used?
With appropriate permissions, your samples and collected information may also be shared with other researchers here, around the world, and with companies. Your samples will be stored in a UTSW biorepository (IMPACT) indefinitely. Your samples will be labeled with a code and not with your name or other information that could be used to easily identify you.

By agreeing to participate in this study, your information or tissue samples could be used for future research studies or sent to other investigators for future research studies without additional consent from you. The information that identifies you will first be removed from your information or tissue samples. If you do not want your information or tissue samples to be used for future research studies without your consent, you should not participate in this study.

Information about NIH Data Archive – "What happens to your research data?"

Data from this study will be submitted to the NIMH Data Archive (NDA) at the National Institutes of Health (NIH). NDA is a large database where de-identified study data from many National Institute of Mental Health (NIMH) studies is stored and managed. De-identified study data means that all personal information about you (such as name, address, birthdate, and phone number) is removed and replaced with a code number. Sharing your de-identified study data helps researchers learn new and important things about mental health and substance use more quickly than before.

During and after the study, the study team will send de-identified study data about your health and behavior to the NDA. Other researchers across the world can then request your de-identified study data for other research. Every researcher (and institutions to which they belong) who requests your de-identified study data must promise to keep your data safe and promise not to try to learn your identity. Experts at the NIH who know how to keep your data safe will review each request carefully to reduce risks to your privacy. Sharing your study data does have some risks, although these risks are rare. Your study data could be accidentally shared with an unauthorized person who may attempt to learn your identity. The study researchers will make every attempt to protect your identity.

You may not benefit directly from allowing your study data to be shared with NDA. The study data provided to NDA may help researchers around the world learn more about mental health and substance use and how to help others who have problems with mental health and substance use. NIMH will also report to Congress and on its website about the different studies using NDA data. You will not be contacted directly about the study data you contributed to NDA.

You may decide now or later that you do not want your study data to be added to the NDA. You can still participate in this research study even if you decide that you do not want your data to be added to the NDA. If you know now that you do not want your data in the NDA, please tell the study researcher before leaving the clinic today. If you decide any time after today that you do not want your data to be added to the NDA, call or email the study staff who conducted this study, and they will tell NDA to stop sharing your study data. Once your data is part of the NDA, the study researchers cannot take back the study data that was shared before they were notified that you changed your mind. If you would like more information about NDA, this is available on-line at http://nda.nih.gov.

Contact Information – Who can you contact if you have questions, concerns, comments or complaints?

Please see your Local Context Information Sheet (Part 2) for contact information for your study site. If you have questions now, feel free to ask researchers at your site. If you have additional questions, concerns, comments, or complaints later or you wish to report a problem or injury which may be related to this study please contact the individuals listed on your Local Context Information Sheet (Part 2).

The University of Texas Southwestern Medical Center Human Research Protection Program (HRPP) oversees research on human subjects. HRPP and Institutional Review Board (IRB) representatives will answer any questions about your rights as a research subject, and take any concerns, comments, or complaints you may wish to offer. You can contact the HRPP by calling the office at 214-648-3060.