Adult Participant Consent Form

Study Title: Open-Label Intravenous Subanesthetic Ketamine For Adolescents With Treatment-Resistant Depression

Study #: CTSI 22225

Study Doctor: Kathryn Cullen, MD
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You are invited to enroll in a research study that will use a drug called ketamine as a potential antidepressant treatment. Before agreeing to participate in this study, it is important that you read this consent form. This form may contain words that you may not understand. Please ask one of the study team members to explain any information that is not clear. You may take as much time as you wish to make up your mind about whether or not you would like to participate. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

This study is being conducted by Dr. Kathryn Cullen and her colleagues in the Department of Psychiatry at the University of Minnesota (UMN). It is funded by the Clinical and Translational Science Institute at UMN. We hope to enroll about 20 people aged 12-18 years at the University of Minnesota.

Why is this study being done?

This study will try to learn if a drug called ketamine can be used to help adolescents with treatment-resistant depression. Ketamine is investigational in this study, which means it is not approved in the United States for adolescent treatment-resistant depression by the U.S. Food and Drug Administration (FDA).

How long will the study last?

Participation in this study may last up to 9 weeks, and we may also contact you after 6 months for a brief follow-up interview.

What is involved in the study?

The following information describes what will happen if you agree to participate in the study.

We will ask you to participate in a clinical assessment, including a physical exam if you have not had one within 30 days. We will ask questions about your medical and psychiatric history, and ask you to complete questionnaires about your symptoms, including any thoughts of hurting

yourself or others. We also test the urine for the presence of certain drugs. The study doctor or study staff will tell you if the drug test results are positive. The results of the drug test must be negative in order for you to be in the study.

Due to unknown risks and potential harm to an unborn fetus, we will not include anyone who is pregnant in the study. Females who can have children will be asked to give a urine sample for a pregnancy test. The study doctor or study staff will tell you if the pregnancy test results are positive. The results of the pregnancy testing must be negative to participate in the study.

We will ask you to have Magnetic Resonance Images (MRI) of the brain. This will take place on a 3 Tesla MRI scanner at the Center for Magnetic Resonance Research (CMRR) at the University of Minnesota. This involves lying quietly inside the center of a large doughnut-shaped magnet. To help you keep still during the MRI, we will place foam pillows around your head. We will perform several different kinds of scans, including scans while you are at rest and scans during an "emotion task", during which you will look at pictures/words and decide whether they are positive or negative.

The entire MRI procedure will take about 2 hours. We will do this before and after the 2-week ketamine dosing. We will ask you to provide your own transportation to the CMRR. If you are admitted to the inpatient mental health unit on the day of the scan, you will need a pass written by your regular physician to allow you to leave the hospital to complete this visit. If either you or your regular doctor do not feel comfortable with having you go on a pass for this MRI visit, this part of the study does not need to happen.

The ketamine infusions take place at University of Minnesota Masonic Children's Hospital in the Journey Clinic. You will complete several questionnaires about how you are feeling, and these are repeated throughout the session. Then we will place a tube, or IV (intravenous—directly into the vein) catheter, in your non-dominant arm to administer the ketamine at a dose of 0.5 mg/kg. The dose is based on your weight. We will measure heart rate and other vital signs (blood pressure, breathing rate and oxygen saturation) throughout the visit. The entire infusion will last 40 minutes. You will stay another 2 hours after the infusion to be monitored for comfort and safety. The ketamine infusions will follow a Monday, Wednesday, Friday schedule for a total of 6 infusions over 2 weeks.

Participants will undergo a blood draw (20 mL, or about a tablespoon) three times in the study, once before and once after the first ketamine infusion, and once after the last infusion. The blood samples will be sent to the Mayo Clinic in the laboratory of Susannah Tye, Ph.D. for analysis.

At two visits during the study (at the beginning of the study and after the last infusion), you will be asked to take a “dot pattern expectancy” task, which will measure your ability to follow visual cues using simple dot patterns.

We will re-assess your depression after the 6 doses of ketamine.

- In the event you no longer wish to participate, you will be referred back to your regular physician for treatment. If you did not have established care for depression we will refer you to an appropriate provider. We will provide recommendations as to level of care (for example, inpatient vs. outpatient, time to next visit if outpatient). If inpatient care is needed, we will work with you to facilitate this. If safety is an immediate concern, we will escort you to the emergency room, which is located one floor below the research facility where your interviews will take place. We will also possibly share the study information

with your treating physician. If you would like us to do this, we will ask you to sign a release of information to allow us to contact your treating physician and share the information and our recommendations.

- If you wish to continue the study, you will participate in 6 weekly follow-up visits for a brief interview and to complete questionnaires about how you are feeling. If depression returns before the sixth visit, you will exit the study at that time. Procedures for transitioning you to an ongoing provider will then be identical to those outlined above.
- We will also contact you after 6 months from the last day of your participation in the above activities in order to arrange a brief (approximately 30 minute) interview, either in person or by video conference, to assess your progression during the intervening time period. This encounter will be similar to the follow-up visits in content and duration.

Any urine samples taken during the study will be used for the testing described above, and then discarded when the results are available. There are no plans to store these urine samples.

Your blood samples will be identified only with your study code number.

All biological samples will be destroyed at the end of the study. Be aware that if you change your mind about being in the study, your blood samples may or may not be withdrawn from the research, depending on the study center's policies. You can ask the study doctor or study staff if you have questions about this.

While you are in the study, you must:

- Follow the instructions you are given.
- Come to the study center for all visits with the study doctor or study staff.
- Tell the study doctor or study staff about any changes in your health or the way you feel.
- Tell the study doctor or study staff if you want to stop being in the study at any time.

What are the possible risks?

Effects of ketamine during infusion may include:

- feeling detached from surroundings
- reduced concentration
- feeling as if in a dream
- colors or sounds seeming brighter or duller than usual
- blurred vision
- decreased pain
- increased anxiety
- euphoria (feelings of extreme happiness)
- confusion
- hallucinations
- sweating
- increased blood pressure
- increased heart rate
- rash
- nausea
- vomiting

Ketamine at lower doses, such as those used in this study, may have side effects that are mild, and only last for a short period of time. These effects include:

- memory impairment
- dizziness
- increased libido
- gastrointestinal distress
- increased thirst
- headache
- metallic taste
- constipation

Some subjects have reported a "hangover" on the day after ketamine administration, and some report vivid dreams for a few days afterward.

At higher doses, ketamine can affect vital signs such as blood pressure and heart rate. We will monitor vital signs. Ketamine infusions will be administered with supervision in the Journey Clinic as a day procedure. Pulse, breathing rate, and blood pressure will be continually monitored. If a severe or unexpected adverse event occurs, you will be evaluated to determine the need for any of the following: stopping the ketamine, changing other drugs, or providing medical care.

Please tell the study doctor or study staff right away if you have any side effects. Please tell them if you have any other problems with your health or the way you feel during the study, whether or not you think these problems are related to the study.

It is possible that receiving ketamine may change how your regular medications, vaccines, or supplements work. It is very important that you tell the study doctor about any medications, supplements, or vaccines before you take them during the study.

You may be given medications during and after the ketamine infusions to help treat or prevent side effects. You should ask the study doctor or study staff about the risks of these medications.

Sometimes people have allergic reactions to drugs. If you have a very bad allergic reaction, you could die. Some things that happen during an allergic reaction that could be a sign or symptom of a life-threatening allergic reaction (anaphylaxis) are:

- a rash
- a fast pulse
- sweating
- a feeling of dread
- swelling around the eyes and mouth
- swelling of the throat
- wheezing
- having a hard time breathing
- a sudden drop in blood pressure (making you feel dizzy or lightheaded)
- inability to breathe without assistance

You should get medical help and contact the study doctor or study staff if you have any of these or any other side effects during the study.

There are risks associated with use of the high field MRI system.

- *Claustrophobia.* Some people experience claustrophobia (fear of confined spaces) while inside the scanner. Use the squeeze bulb to let us know immediately if you are experiencing claustrophobia, and we will terminate the scan.
- *Magnetic pull of metal objects.* Objects with magnetic properties can be pulled into the magnet. Also, an MRI could be very dangerous if you have certain objects or devices implanted in your body, such as a pacemaker, insulin pump, ear implant, joint replacement, permanent dentures, piercings, or shrapnel. You must tell the study doctor or study staff about any objects that you know are implanted or embedded in your body.
- *Energy from the scanner can cause heating or nerve stimulation.* Another risk is presented by the energy waves used in the scanner. The power of the energy waves is well below the strength needed to heat the tissue in your body and cause harm, but any metal in contact with your skin could heat up. This is why you will be asked to remove all jewelry. If you have metal on your body that cannot be removed, we will review this with you carefully, and it may be that you will not be able to participate in the study. It is also possible that the scanner will cause peripheral nerve stimulation (stimulation of the nerves or muscles). If you feel any tingling or unusual sensations during the scan, or muscle contractions, use the squeeze bulb to alert the researcher immediately.
- *Scanner noise.* The noise generated by the operation of the scanner during a study is loud enough to cause hearing damage if you do not wear hearing protection, which we will provide. If, even with the hearing protection we give you, you find the noise from the scanner to be uncomfortable or painful, you should ask the scanner operator to stop the scan immediately.
- *Unknown long-term risks.* In addition, there is a risk of unknown effects related to participation in 3 Tesla MRI research. Long-term effects of exposure to high magnetic fields are unknown.
- *Short-term symptoms.* Short term, most people experience no ill effects from the strong magnetic field, but some people report dizziness, mild nausea, headache, a metallic taste in their mouth, or sensations of flashing lights. These symptoms, if present, become less intense shortly after leaving the magnet. If any sensations experienced during participation cause discomfort or pain, notify the researcher right away and your scan will stop and you will be taken out of the magnetic field.
- *Risks related to pregnancy.* The risks of exposure to high magnetic fields are unknown for fetuses. Therefore, we will not include anyone in the study who is pregnant, as measured by a urine pregnancy test.
- *Potential for discovery of brain abnormalities.* It is possible that the MRI scan would reveal unknown and unlooked for abnormalities in your brain. We routinely have each scan sent to a radiologist (a doctor who specializes in looking at these images), and if there are abnormalities we will let you know of these results. We will provide your regular physician with a copy of these images if you would like.

The risks of drawing blood and putting an I.V. catheter in your arm include dizziness, pain, bruising, or infection at the site of the needle stick. Infections happen rarely.

In addition, problems you could have from I.V. administration of ketamine directly into your vein include:

- irritation of the vein; your skin near the vein could become warm, swell, hurt, or get red
- damage to your vein
- damage to the skin or tissue around the injection site

- too much of the ketamine may be given to you
- increase or decrease in electrolyte levels (the amount of certain salts and other chemicals in your blood), causing health problems
- a blood clot or an air bubble could form, which could block a blood vessel in another part of your body

Some of these problems could be very serious.

Over time, getting a lot of injections can cause a vein to become hard or scar, which can make it difficult to put a needle into the vein to give you a shot or take blood.

If you are pregnant or nursing a child while receiving ketamine, there may be risks to your unborn baby or nursing child. Some drugs cause premature (early) birth or birth defects. Nobody knows what all of these risks are right now.

If you are a woman who can have children, the study doctor or study staff will talk to you about birth control you must use during the study.

If you think you are pregnant during the study, you must tell the study doctor or study staff immediately. Women who become pregnant during the study will have to leave the study.

Some of the questions you will be asked in the study questionnaires may make you feel uncomfortable or upset. Please tell the study doctor or study staff if you feel uncomfortable or upset while answering the study questionnaires. You do not have to answer any question that makes you uncomfortable or upset.

There is a risk of loss of confidentiality of your information. You will read more about the protection of your information later in this form. Please ask the study doctor or study staff if you would like to know more about how your information will be protected while you are in this study.

There may be other unknown side effects that could occur, which include your depression getting worse.

Ask the study doctor if you have questions about the signs or symptoms of any side effects that you read about in this consent form.

Are there any potential benefits?

With ketamine, it is possible that you may experience a reduction in depressive symptoms and improvement in social and family functioning. However, this is not guaranteed and there may be no direct benefit to you from being in the study. The knowledge gained from this study may benefit others in the future.

What other options are there?

You do not have to be in this study to get help for your treatment-resistant depression. You can choose to not participate in this study. You can continue to work with your current provider to manage depression.

You should discuss your alternatives to participating in this research with the study doctor or study staff. In addition, you may discuss your options with your regular health care provider.

What are the costs?

Participation in this study will be at no cost to you.

Will I get paid?

You will be compensated up to $220 for your participation at different time points: $40 for the initial visit, $20 for the post infusion clinical visit, $40 after each MRI assessment (total of 2), $20 for the 6 month visit, and $10 for each of the weekly follow-up visits (up to 6). There will be no reimbursement for the ketamine infusion visits. If you start, but do not finish the study, monetary compensation will be pro-rated according to each completed visit.

In addition to study payment, you will also be reimbursed for parking at the study center, up to a total of $126 for the entire study.

What will happen if there is a research-related injury?

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to you or your insurance company. If you think you have suffered a research related injury let the study doctor or study staff know right away.

You do not give up any of your legal rights by signing this form.

Be aware that your health care payer/insurer might not cover the costs of study-related injuries or illnesses.

Will medical information be kept private?

The records of this study will be kept private. In any publications or presentations, you will not be identified by name or other recognizable way on any records, results or publications relating to the study. Your medical records, as they relate to the research study, may be reviewed by the U.S. Food and Drug Administration, CMRR personnel, other regulatory authorities, and Quorum Review (a group of people who review research studies to protect the rights and welfare of research participants) to check trial data and procedures and ensure that the information is accurate.

Any information obtained in connection with this study that can be identified with you will remain confidential and will be disclosed only with your permission. However, mental health professionals are mandated reporters, which means that we are obliged to report alleged or probable abuse, as well as known abuse. If there are any concerns about maltreatment, they will be reported in accordance to the law. If you tell us that someone (including yourself) is in danger of serious harm, we may need to obtain outside assistance.

Only researchers associated with this study and other authorized personnel will have access to the records; research records will be kept in a locked file. In any sort of report we might publish, we will not include any information that will make it possible to identify you.

Your protected health information created or received for the purposes of this study is protected under the federal law known as HIPAA. This means that we must keep your medical information

private and confidential to the greatest extent possible. Your protected health information includes contact information or any identifying information. You will be asked to review and sign a separate HIPAA authorization form concerning the use of this information.

To these extents, confidentiality is not absolute.

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.

Incidental Findings

The images or pictures created during this study are for research purposes only and are not intended to provide health care to you. However, if the results from the magnetic resonance imaging show something unusual in the pictures, a Radiologist trained in reading the pictures will look at them. The Radiologist would not receive any personal information except your age and pertinent medical history collected as part of the research. There will be no charge to you for having the Radiologist look at your pictures. The investigator in charge of this study will contact you if the recommendation of the Radiologist is to further investigate the unusual results of the pictures with your own physician. However, further medical follow up is not a part of this study and the study does not have funds set aside for this purpose. Therefore, if the results do show something unusual, any medical follow up cost will be your responsibility and/or the responsibility of your health insurance carrier.

What are your rights as a research subject?

Your decision to take part in this study is voluntary. You have the right to decide not to participate. Should you agree to participate in this research, you may change your mind at any time and withdraw yourself from the study. A decision not to participate will not harm your relationship with the study doctors and the study staff, nor will it affect your regular treatment in any way. Deciding not to be in this study or changing your mind later will not result in any penalty to you, and you won't lose any benefits except for benefits having to do with the study.

The study doctor may withdraw you from the study without your consent at any time if: he or she believes it is in your best interest (for example, if your condition is worsening, and a treatment option outside of the study is available that would be better for you); you significantly fail to follow study directions and procedures; or if there are unexpected or serious side effects.

If you stop being in the study early, the study doctor or study staff may ask you some questions about being in the study. The study doctor or study staff may ask you to participate in some procedures or tests to help you leave the study safely and/or to collect more information for the study. If you leave the study, the study doctor and study staff will still be able to use your information that they have already collected.

What if new information becomes available about the study?

The study doctors will notify you if there are new findings that might affect your willingness to continue to be in the study, or that could affect your health either during or after the study.

Who can you call if you have questions about the study?

In the event of an emergency, dial 911 immediately.

If you require emergency care, be sure to tell the emergency care provider about your participation in this study. Contact the study doctor or study staff as soon as possible.

You can ask questions about the study at any time. You can call the study doctor or study staff at any time if you have any concerns or complaints. You should call the study doctor or study staff at the phone number listed on page 1 of this form if you have questions about the study procedures, study costs (if any), study payment (if any), or if you get hurt or sick during the study.

Quorum Review reviewed this study. Quorum Review is a group of people who review research studies to protect the rights and welfare of research participants. Review by Quorum Review does not mean that the study is without risks. If you have questions about your rights as a research participant, if you are not able to resolve your concerns with the study doctor or study staff, if you have a complaint, or if you have general questions about what it means to be in a research study, you can call Quorum Review or visit the Quorum Review website at www.quorumreview.com.

Quorum Review is located in Seattle, Washington.
Office hours are 8:00 AM to 5:00 PM Pacific Time, Monday through Friday.
Ask to speak with a Research Participant Liaison at 888-776-9115 (toll free).

You will be given a signed copy of this form to keep for your records.

Permission to Videotape

We are asking your permission to videotape certain portions of the study during visits and ketamine infusions. You do not have to let the study doctor or study staff videotape you if you don't want to. You can still be in the study if you do not want to be videotaped. You can ask the study doctor or study staff questions about it before you decide if you want to let them videotape you.

If you agree to be videotaped, the videotape will be used by individuals directly involved in the study for research purposes in order to ensure the reliability of the diagnoses and assessments.

Videotapes may also be presented to individuals such as medical students and residents for educational purposes. (We will not provide your name.)

The videotapes will show your whole body. It is possible that people who see the videotapes will recognize you.

If you change your mind later, tell the study doctor or study staff. Be aware that any videotape taken before you changed your mind may still be used and shared as described in this form.

You will indicate your choice about being videotaped at the end of this form.

Permission to Share Data Outside the Study

The data that you provide is valuable and could be useful for other studies of adolescent health problems. When individuals provide consent to be in a research study, they are consenting for their information to be used only for the purpose of that study. The data cannot be combined with data from other studies. Investigators who focus on clinical samples do not always have easy access to comparison groups. Therefore, we request your consent to use your data in the context of other studies where Dr. Cullen is a co-investigator. We need to know if this is okay with you. If you agree to have your data shared across studies, your data will be grouped with that of other study participants for comparison with groups from other studies (for example, other groups of people with depression or other conditions, other healthy groups, groups of different ages). Data to be shared may include results from any of the tests that are described above in the study procedures. We will not share your name, address, or other contact information.

You will indicate your choice regarding data sharing at the end of this form.

Permission for Future Re-Contact

The study team wants to know if you will allow the members of the study team to contact you in the future to request information about your progress, and possibly to request further participation in an expanded portion of this study. Allowing the study team to contact you again does not obligate you to join any study or take part in any activities. If you do not want to allow this contact, you can still be in the study. If you agree now, you can change your mind at any time.

You will indicate your choice regarding future re-contact at the end of this form.

Statement of Consent

I have read the above information. I have asked questions and have received answers. I voluntarily consent to participate in the study.

By signing this form, I do not give up any of my legal rights. I will get a signed copy of this consent form.

Permission to Videotape: Please initial <u>one line</u> regarding videotaping of study visits as described above:

_____ I agree to allow portions of the visits to be videotaped for research purposes.

_____ I do not agree to be videotaped. I can still be in the study.

Permission for Data-Sharing: Please initial one line regarding data-sharing as described above.

_____ I agree to have my data shared with other studies where Dr. Cullen is a co-investigator. I may withdraw this consent to share data at any time in the future by contacting Dr. Cullen at (612)-273-9711.

_____ I do not agree to have my data shared with other studies. I can still be in the study.

Permission for Future Re-Contact: Please initial one line regarding your choice to be contacted in the future as described above.

_____ I agree to be re-contacted.

_____ I do not agree to be re-contacted. I can still be in the study.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

I attest that the individual providing consent had enough time to consider this information, had an opportunity to ask questions, and voluntarily agreed to participation in this study.

_____
Printed Name of Person Explaining Consent

_____ _____
Signature of Person Explaining Consent Date