DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
ADULT
A Double-Blind, Placebo-controlled, Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) Study of the Safety, Pharmacokinetics and Pharmacodynamics of (2R,6R)-Hydroxynorketamine in Healthy Volunteers

The purpose of this Phase 1 study is to establish if the study drug (2R,6R)-Hydroxynorketamine HCl is safe to be given to humans. A second goal is to see how much of the study drug stays in human blood after it is given to participants. This will be the first time (2R,6R)-Hydroxynorketamine HCl is given to humans. This study drug is not yet approved by the Food and Drug Administration (FDA) for use other than in research studies such as this.

Healthy adults ages 18-65 can participate in this study. If enrolled, you will undergo screening procedures to see if you qualify. If you qualify and wish to continue, you will be asked to return to the Duke Early Phase Clinical Research Unit (DEPRU) for an overnight stay. The length of your stay will depend on which of the two parts of the study you are enrolled in. The study drug will be given intravenously [(IV) a slow injection into a vein]. Study participants in Part 1 of the study will receive a single dose of the study drug or placebo (an infusion that does not contain the study drug) and stay overnight for 2 nights. Study participants in Part 2 of the study will receive multiple doses of the study drug or placebo and stay overnight for 11 nights. Tests, exams, and procedures will be performed on you as part of the study.

As with all clinical studies, there are risks. You may experience momentary discomfort and/or bruising from blood draws. Since this will be the first time the study drug is given to humans there may be risks, discomforts, or side effects of (2R,6R)-Hydroxynorketamine that are currently unknown.

If you are interested in learning more about this study, please continue reading below.

You are being asked to take part in this research study to help find better antidepressant drugs. Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your 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. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

Please tell the study doctor or study staff if you are taking part in another research study.

A grant from the National Institute of Mental Health (NIMH) will sponsor this study. Portions of Dr. Guptill's and his research team's salaries will be paid by this grant.

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WHO WILL BE MY DOCTOR ON THIS STUDY?

If you decide to participate, Dr. Jeffrey Guptill will be your doctor for the study and will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed.

WHY IS THIS STUDY BEING DONE?

The study is being done to assess the safety and tolerability of the investigational study drug, (2R, 6R)-Hydroxynorketamine HCl. This is the first time that (2R, 6R)-Hydroxynorketamine HCl will be given to humans. "Investigational" means the drug is being tested for safety and effectiveness and has not been approved by the FDA (U.S. Food and Drug Administration) for use in the United States other than in research studies such as this. In this informed consent form, the investigational drug will be referred to as (2R, 6R)-Hydroxynorketamine or study drug. The study will also measure how the study drug moves through the bloodstream after it is given and how long it takes for the body to remove the study drug from the bloodstream.

(2R, 6R)-Hydroxynorketamine is being studied as a possible antidepressant treatment in patients with treatment-resistant depression. Ketamine, a drug that is currently used for treatment-resistant depression has side effects including drowsiness, loss of pain, temperature sensation and addiction or abuse potential. (2R, 6R)-Hydroxynorketamine in animal models has demonstrated the antidepressant qualities of ketamine without the side effects including a lack of addiction or abuse potential.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Approximately 72 healthy study participants, male and female, 18-65 years of age, will take part in this study at Duke. Duke is the only site for this study.

WHAT IS INVOLVED IN THE STUDY?

If you decide to participate in this study, you will be asked to sign and date this consent form. You will then undergo screening procedures to see if you qualify. If you qualify and wish to continue, you will be asked to return to the Duke Early Phase Clinical Research Unit (DEPRU) for an overnight stay. The length of your stay will depend on which of the two parts [Part 1: Single Ascending Dose (SAD), or Part 2: Multiple Ascending Dose (MAD)] of the study you are enrolled in. Study participants in the SAD study will stay overnight for 2 nights. Study participants in the MAD study will stay overnight for 11 nights. You will be told at the time that you sign the consent which part of the study (SAD or MAD) you will be participating in.

Both parts of the study will include the following processes: screening, admission for confinement to DEPRU, dosing with the study drug or placebo (a placebo looks like the study drug, but does not have any active ingredients in it), and follow-up visits. During screening and prior to admission into the in-patient clinic, study staff will interview you to confirm you are able to participate, obtain a detailed

medical history, and perform screening assessments as outlined below. Upon admission for confinement to DEPRU, similar assessments as in the screening visit will be performed to ensure that you continue to meet eligibility criteria prior to dosing. On dosing day, you will receive either the study drug or placebo and we will monitor any changes in your health. Blood and urine samples will also be obtained. During follow up, we will continue to monitor changes in your health.

After signing and dating this consent document, the following screening procedures will be done to determine if you qualify for this study. The screening visit will take about 2-3 hours.

Screening Visit

- Physical exam (including height, weight, & body mass index (BMI))
- Medical history (including prescription & over the counter medications)
- Vital signs
- Blood collection
  - Routine lab tests to check your health
  - Pregnancy test for females of childbearing potential
  - Hepatitis B and C*
  - HIV*

  **Note: As part of this protocol, you will be tested for HIV (human immunodeficiency virus, which is the virus that causes the acquired immunodeficiency syndrome [AIDS]), hepatitis B, and hepatitis C. You will be notified of the results of the testing, and counseled as to the meaning of the results, whether they are positive or negative. If the test indicates that you are infected with HIV, hepatitis B, or hepatitis C you will receive additional counseling about the significance of your care and possible risks to other people. We are required to report all positive results to the North Carolina Division of Public Health. The test results will be kept confidential to the extent permissible under the law. If you do not want to be tested for HIV, hepatitis B, or hepatitis C then you should not agree to participate in this study.*
- Urinalysis
- Urine drug screen; including *cotinine
  **(cannot use tobacco or nicotine containing products 4 weeks prior to investigational agent administration)*
- Electrocardiogram (ECG), a tracing of the electrical activity of the heart
- Breathalyzer (test for presence of alcohol)
- Questionnaire (mental health assessment). We will be screening for suicide risk.

If you continue to qualify for the study and you wish to continue participation, you will be assigned to one of the two parts (SAD or MAD). SAD means Single Ascending Dose, and in this part of the study, participants receive the investigational agent a single time and starting with the smallest dose. The dose is increased if there are no serious side effects. MAD means Multiple Ascending Dose. In this part of the

study, study drug will be given a total of 4 times over a two week period if we do not see any serious side effects in the first part of the study. You will be randomly selected (like a flip of the coin) to receive either study drug or placebo. Neither you nor the study doctor will know if you are randomized to receive study drug or placebo.

In the SAD study, two study participants (sentinel subjects) of each group will be randomized and given study drug before the rest of the group. For each sentinel pair, one study participant will receive the study drug, and one will receive placebo. Once the sentinel group has received study drug , a review of safety data will be completed over at least 24 hours prior to the remaining study participants receiving study drug. Of the remaining study participants in the cohort, five will receive study drug and one will receive the placebo. The study team will then monitor all subjects for safety for at least three days before progressing to the next dose level. At that point the process is repeated all over again in the same manner for each of the remaining 5 dose levels.

If you participate in Part 1 (SAD), you will receive a single dose of study drug or placebo following an overnight fast. There will be six groups or cohorts in Part 1. See the table below for the groups and dose levels in Part 1.

SAD planned dosing levels

Cohort	Dose (mg/kg)	Study Participants on Investigational Agent (n)	Study Participants on Placebo (n)
1A (Sentinel 1)	0.1	1	1
1B	0.1	5	1
2A (Sentinel 2)	0.25	1	1
2B	0.25	5	1
3A (Sentinel 3)	0.5	1	1
3B	0.5	5	1
4A (Sentinel 4)	1.0	1	1
4B	1.0	5	1
5A (Sentinel 5)	2.0	1	1
5B	2.0	5	1
6A (Sentinel 6)	4.0	1	1
6B	4.0	5	1

If you participate in Part 2 (MAD), you will receive multiple doses of study drug or placebo. You will receive a total of four doses of study drug or placebo given on Days 1, 4, 7, and 10. Each dose is

following an overnight fast (no food or drink). You will only receive a single dose level of the study drug or placebo. There will be three groups of study participants in Part 2. See the table below for the groups and dose levels in Part 2. The highest dose administered in the MAD will not exceed the highest determined tolerable SAD dose.

MAD planned dosing levels

Cohort	**Dose (mg/kg)**	**Study** Participants **on Investigational agent (n)**	**Study** Participants **on Placebo (n)**
1	0.5	6	2
2	1.0	6	2
3	2.0	6	2

WHAT DO I HAVE TO DO?
While you are in the study you must:

- Not take part in any other medical research studies
- Give correct and accurate information about your medical history and current medications
- Agree to the following restrictions:
    - You must remain at DEPRU until 24 hours after you receive study drug (SAD group) or 24 hours after receiving the final study drug (MAD group).
    - You must continue using appropriate method of birth control from screening to 90 days after end-of-study
    - You must avoid excess daily eating of certain foods and drinks during your stay at DEPRU. These include:
        - Chocolate (> 1 serving or 1.55 ounces)
        - Coffee (> 3 cups or 0.7 liters)
        - Caffeinated teas (>3 cups or 0.7 liters)
        - Caffeinated colas (>3 cups or 0.7 liters)
    - You must avoid drinking beverages or eating food that contain alcohol, grapefruit, poppy seeds, Brussels sprouts, pomegranate, broccoli, char-grilled meat within 2 days prior to receiving study drug.
    - You must eat standard hospital meals during your DEPRU stay. Eating excessive amounts of food is not permitted
    - You must not use tobacco or nicotine containing products including (but not limited to):
        - cigarettes

- e-cigarettes
- nicotine patches
- cigars
- bidis
- kreteks
- pipes
- chewing tobacco
- snuff
- dip

- You must not use drugs of abuse including (but not limited to):
  - alcohol
  - cannabinoids (marijuana)
  - opiates
  - cocaine
  - amphetamines
  - benzodiazepines
  - hallucinogens
  - barbiturates
- You must not perform strenuous exercise during your DEPRU stay and for 48 hours after completion of the final does of study drug.
- You must not donate blood for at least 90 days after the completion of the study or participate in any investigational drug study for at least 90 days after completion of the study.

Part 1 – (SAD)
Day -1 Admission & Confinement
Within 28 days of your screening visit, you will be scheduled to return to DEPRU to be admitted for the confinement period (overnight stay). If you participate in Part 1, you will stay overnight at the DEPRU for 2 nights (3 days).

Study participants will arrive at the DEPRU on the day prior to receiving study drug in the morning. The following procedures will occur:

- Review of eligibility criteria
- Physical exam (including weight, & BMI)
- Medical history (including prescription & over the counter medications)
- Vital signs
- Blood collection
  - Routine lab tests to check your health
  - Urine pregnancy test for females of childbearing potential

- Urinalysis
- Urine drug screen; including *cotinine
  **(cannot use tobacco or nicotine containing products 4 weeks prior to the investigational agent administration)*
- Electrocardiogram (ECG*),* a tracing of the electrical activity of the heart
- Breathalyzer (Alcohol screen test)
- Eye exam (including test for clearness/sharpness of vision as well as a color vision test)
- Questionnaires (mental health assessments)

Study Drug- Part 1
The morning after your admission, following the overnight fast, you will receive a single dose of either study drug or placebo by IV infusion (through a vein)

On Day 1, you will also have blood drawn for pharmacokinetics (PK) tests. Pharmacokinetics (PK) is what the body does to a drug, including the movement of the drug into, through, and out of the body. PK tests will be done at the following times: pre-dose, end-of-infusion, 1, 2, 4, 8, 12, 24 and 48 hours after the start of infusion. In addition, blood and urine will be collected for routine lab tests. The total volume of blood drawn will be 109 mL (about 7 tbsp.). PK urine samples will be collected during the SAD study for each study participant receiving study drug and placebo at set intervals following the initiation-of-infusion (0-4, >4-8, >8-12, >12-24 hr.). Study participants will be watched for adverse effects (AEs) from time they receive study drug until end-of-study. The following activities will also be performed at Screening (Day –28 to Day -2), Day -1, Day 1, Day 2, Day 3 and Day 5-8: vital signs (blood pressure, sitting heart rate, temperature, and respiratory rate, ECGs (records electrical signals from your heart), electroencephalogram [(EEG) a tracing of the electrical activity of the brain], and questionnaires (mental health assessments).

Approximately 24 hours after you are given study drug, you will be discharged. Before you are discharged from the DEPRU, the following activities will be completed:

- Physical exam
- Vital signs
- Blood and urine collection for routine lab tests
- Electrocardiogram (ECG), a tracing of the electrical activity of the heart
- Review of medications
- Blood and urine samples for PK analysis
- Questionnaires (mental health assessments)
- Review of Adverse effects

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Follow-up (DAY 3)
You will return to DEPRU on DAY 3, approximately 48 hours after you received study drug. The following procedures will be performed:

- Physical exam (including weight, & BMI)
- Electrocardiogram (ECG), a tracing of the electrical activity of the heart
- Review of medications
- Eye exam (including test for clearness/sharpness of vision as well as a color vision test)
- Blood sample for PK analysis
- Review of Adverse Events (AE)

Follow-up (DAY 5-8)
You will receive a telephone call from research staff to review your medications and any AEs (side effects) that you may have experienced and be asked questions about your mental health.

Part 2 – (MAD)
Day -1 Admission & Confinement
Within 28 days of your screening visit, you will be scheduled to return to DEPRU to be admitted for the confinement period (overnight stay). If you participate in Part 2, you will stay overnight at the DEPRU for 11 nights (12 days).

Study participants will arrive at the DEPRU the day before you receive study drug in the morning. The following procedures will occur:

- Review of eligibility criteria
- Physical exam (including weight, & BMI)
- Medical history (including prescription & over the counter medications)
- Vital signs
- Blood collection
  - Routine lab tests to check your health
  - Urine pregnancy test for females of childbearing potential
- Urinalysis
- Urine drug screen
- Electrocardiogram (ECG), a tracing of the electrical activity of the heart
- Breathalyzer (Alcohol screen test)
- Eye exam (including test for clearness/sharpness of vision as well as a color vision test)
- Questionnaires (mental health assessments)

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Study Drug – Part 2
After your admission, you will receive a single dose level of either study drug or placebo by IV infusion (through the vein) on DAYs 1, 4, 7 and 10. Each dose will follow an overnight fast (no food or drink).

Serial PK blood and urine samples will be collected for the first and fourth (last) dosing in the MAD study for each study participant receiving the study drug and placebo. You will also have blood drawn for PK assessments on Days 1, 4, 7 and 10 pre-dose. On Days 1 and 10 PK assessments will also be done at the following time points: at the end-of-infusion, and at 1, 2, 4, 8, 12, 24 and 48 hours after the start of infusion. In addition, blood and urine will be collected for routine lab tests. The total volume of blood drawn will be 219 mL (about 15 tbsp.). PK urine samples will be collected during the MAD study for each study participant receiving the study drug and placebo at set intervals following the initiation-of-infusion (0-4, >4-8, >8-12, >12-24 hours) after the first and last dose. Study participants will be monitored for Adverse Events (AEs) from time they receive study drug until end-of-study. The following activities will also be completed during your DEPRU stay: vital signs (blood pressure, sitting heart rate, temperature, and respiratory rate, ECGs and questionnaires (mental health assessments).

DAY 11
You will be discharged. Prior to discharge from the DEPRU, the following activities will be completed:

- Vital signs
- Blood and urine collection for routine lab tests
- Electrocardiogram (ECG), a tracing of the electrical activity of the heart
- Review of medications
- Eye exam (including test for clearness/sharpness of vision as well as a color vision test)
- Blood and urine samples for PK analysis
- Questionnaires (mental health assessments)
- Review of Adverse effects

Follow-up (DAY 12)
You will return to DEPRU on DAY 12. The following procedures will be performed:

- Physical exam (including weight, & BMI)
- Vital signs
- Electrocardiogram (ECG), a tracing of the electrical activity of the heart
- Review of medications
- Blood sample for PK analysis
- Questionnaires (mental health assessments)
- Review of Adverse effects

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Follow-up (DAY 17-19)
You will receive a telephone call from research staff to review your medications and any AEs (side effects) that you may have experienced and be asked about your mental health.

HOW LONG WILL I BE IN THIS STUDY?
The amount of time you are in the study will be determined by which section you choose to participate:

SAD:
If you choose to be in this study, your part in the study is expected to last up to 36 days (including the 28-day screening period and 8 days on study with follow-up).

MAD:
If you choose to be in this study, your part of the study is expected to last up to 47 days (including the 28-day screening period and 19 days on study with follow-up).

You can choose to stop participating at any time without penalty or loss of any benefits to which you are entitled. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor first.

I will participate in the following part of the study:

_____ Part 1 – Single Ascending Dose (SAD)

Initials

_____ Part 2 – Multiple Ascending Dose (MAD)
Initials

WHAT ARE THE RISKS OF THE STUDY?
As a result of your participation in this study, you are at risk for the following side effects. You should discuss these with the study doctor and your regular health care provider if you choose.

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(2R,6R)-Hydroxynorketamine
Previous studies in animals using (2R, 6R)-Hydroxynorketamine, suggest that the doses to be used in this study are expected to be safe.

Female
The effect of (2R,6R)-Hydroxynorketamine on the risk of birth defects, miscarriage, or other bad outcomes when taken during pregnancy or while breastfeeding is unknown. To reduce the risk of any harmful effects, women who are pregnant, trying to become pregnant, or breastfeeding are not allowed to participate in studies using (2R,6R)-Hydroxynorketamine.

If you are a woman who could possibly become pregnant (you have not had a hysterectomy and/or both tubes and/or both ovaries removed) and you have a partner who is able to father children, a blood pregnancy test will be performed, and it must be negative to continue in the study. In women 40 years old and older, blood pregnancy tests may sometimes give a false positive or "indeterminate" result, and additional testing may be required to confirm your eligibility for the study. You will also have additional urine pregnancy tests at some study visits, as described above, and they also must be negative for you to continue in the study.

You and your partner must agree to either abstain completely from vaginal intercourse for the duration of the study and for 90 days after your last dose of study drug or use a highly effective method of contraception for the same length of time. Highly effective methods include (a) partner vasectomy, (b) bilateral tubal ligation, (c) intrauterine devices (IUDs), (d) hormonal implants (such as Implanon), or (e) other hormonal methods (birth control pills, injections, patches, vaginal rings) (f) double barrier method (for example, diaphragm with spermicide, condoms with spermicide). If you and your partner are not currently using one of these methods your study doctor will discuss options with you, given your medical condition, your personal preferences, and the level of effectiveness required for this study. Because no birth control method is 100% effective, you should notify your study doctor immediately if you think there is any chance you could be pregnant, even if you have had a recent negative pregnancy test.

If you do become pregnant during the study, your study doctor will stop the study drug withdraw you from the study, and notify the sponsor. You will be followed for the duration of the pregnancy to better understand the potential effects of the study drug on pregnancy outcomes.

Male
It is unknown whether pregnancies that began while the father was taking (2R,6R)-Hydroxynorketamine are at increased risk for birth defects, miscarriages, or other bad outcomes. To reduce the risk of any harmful effects, men who are trying to become fathers are not allowed to participate in studies using the study drug.

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Male participants must agree to one of the following birth control methods from screening to 90 days after end-of-study. (a)Be surgically sterile for at least 90 days before screening. (b)Agree to use a condom with spermicide when sexually active with a female partner who is not using an acceptable method of birth control. (c)Abstinence (with agreement to use a condom with spermicide if they become sexually active during the study).

You should not donate sperm for the duration of the study and for 90 days after the last dose of study drug.

Risks of Drawing Blood
Risks associated with drawing blood from your arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

Risks of IV catheter
The study drug is given through an IV catheter which is a small, flexible hollow tube inserted into a vein in your arm. Inserting an IV requires a needle and can cause localized discomfort. The vein the catheter is inserted in may become inflamed, and there is a risk of infection; however, this is a small risk as aseptic technique will be used.

Risks of Electrocardiogram (ECG)
Possible side effects of the ECG are skin irritation, itching and redness from the ECG electrode pads.

Risks of EEG
Possible side effects of the EEG are skin irritation, itching and redness from the EEG electrode pads.

Drug and Food Interactions
For your safety, you must tell the study doctor or nurse about all the prescribed medical foods and drugs, herbal products, over-the-counter (OTC) drugs, vitamins, natural remedies, and alcohol that you are taking before you start the study and before starting to take any of these products while you are on the study.

There may be risks, discomforts, drug interactions or side effects that are not yet known.

Mental Health questionnaire (C-SSRS) Columbia-Suicide Severity Rating Scale
For your safety if, according to questionnaire, you are actively suicidal you will be taken to Duke University Hospital Emergency Room. If, according to questionnaire, you have considered suicide we will contact your mental health provider (if you have one) or contact a provider at Duke to determine the best approach to address your case.

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ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
While there are no direct benefits to you by participating in this study, we hope that in the future the information learned from this study will benefit other people with treatment resistant depression.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total confidentiality. Your personal information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding, and regulating the study. We will share only the minimum necessary information in order to conduct the research. Your personal information may also be given out if required by law.

As part of the study, results of your study-related laboratory tests, and procedures may be reported to National Institute of Mental Health (NIMH) and its affiliates. In addition, your records may be reviewed to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration (FDA), representatives and affiliates of NIMH, the Duke University Health System Institutional Review Board, and others as appropriate. If any of these groups review your research record, they may also need to review your entire medical record.

The Department of Health and Human Services (HHS) has issued a Certificate of Confidentiality to further protect your privacy. With this Certificate, the investigators may not disclose research information that may identify you in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings, unless you have consented for this use. Research information protected by this Certificate cannot be disclosed to anyone else who is not connected with the research unless:

1) there is a law that requires disclosure (such as to report child abuse or communicable diseases but not for legal proceedings);

2) you have consented to the disclosure, including for your medical treatment; or

3) the research information is used for other scientific research, as allowed by federal regulations protecting research study participants.

Disclosure is required, however, for audit or program evaluation requested by the agency that is funding this project or for information that is required by the Food and Drug Administration (FDA).

You should understand that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not

connected with the research, you must provide consent to allow the researchers to release it. This means that you and your family must also actively protect your own privacy.

Finally, you should understand that the investigator is not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others.

All of the blood and urine studies are being done only because you are in this study. The study results will not be provided to you OR sent to your physician.

The study results will be retained in your research record for at least six years after the study is completed. At that time either the research information not already in your medical record may be destroyed or information identifying you will be removed from such study results at DUHS. Any research information in your medical record will be kept indefinitely.

Some information collected in research studies is maintained in your medical record. However, for this study that information will be inaccessible until the end of the study, unless your physician(s) decide that it is necessary for your care.

This information may be further disclosed by the sponsor of this study. If disclosed by the sponsor, the information is no longer covered by federal privacy regulations.

If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by federal privacy regulations.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your name or other personal information will not be revealed.

Some people or groups who receive your health information might not have to follow the same privacy rules. Once your information is shared outside of DUHS, we cannot guarantee that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect your health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

WHAT ABOUT COMPENSATION?
You will be reimbursed up to $3,675 for your expenses related to your participation (parking, gas, and time). If you withdraw from the study, you will still receive compensation for the parts of the study you completed based on the table(s) below.

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Part 1 - SINGLE ASCENDING DOSE

Visit	Compensation
Screening Visit	$100
Confinement Visit (each of 2 nights)	$300
Discharge / Day 2	$150
Follow-up Visit / Day 3	$100
Follow-up Phone Call / Day 5-8	$25
Total	$975

Part 2 - MULTIPLE ASCENDING DOSE

Visit	Compensation
Screening Visit	$100
Confinement Visit (each of 11 nights)	$300
Discharge / Day 11	$150
Follow-up Visit / Day 12	$100
Follow-up Phone Call / Day 17-19	$25
Total	$ 3,675

Payment received as compensation for participation in research is considered taxable income to the research study participant. If payment to an individual exceeds $600 in any one calendar year, Duke University is required to report this information to the Internal Revenue Service (IRS). Research study participant payments to a non-employee of Duke University exceeding $600 during any calendar year will result in a 1099 (Miscellaneous Income) form being issued to the individual and a copy sent to the IRS.

WHAT ABOUT RESEARCH RELATED INJURIES?
Immediate necessary medical care is available at Duke University Medical Center in the event that you are injured as a result of your participation in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., or your Duke physicians to provide monetary compensation or free medical care to you in the event of a study-related injury. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIMH or the Federal Government.

For questions about the study or research-related injury, contact Dr. Jeffrey Guptill at 919-684-1672 during regular business hours and at 919-684-8111 (ask to have Dr. Guptill paged) after hours and on weekends and holidays.

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
ADULT
A Double-Blind, Placebo-controlled, Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) Study of the Safety, Pharmacokinetics and Pharmacodynamics of (2R,6R)-Hydroxynorketamine in Healthy Volunteers

WHAT ARE THE COSTS TO YOU?
NIMH will provide the study drug free of charge to you. There will be no cost to you for participating in the study. Your study doctor may request that you return for a checkup before you stop your study drug if he thinks that stopping it suddenly may harm you and may ask you to complete the tests that would ordinarily occur when a person completes the study.

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?
You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. Nonparticipation or withdrawal from this study will not affect your job status if you are a Duke employee and will not affect your grades if you are a Duke student nor will it affect any other benefits to which you are entitled. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concern an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record. All data that have already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the study sponsor. Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled and will not affect your access to health care at Duke.

Dr. Guptill may ask you to return for a checkup before you stop your study drug if he thinks that stopping the drug suddenly may harm you.

He may also ask you to complete the tests that would ordinarily occur when a person completes the study.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

Your doctor may decide to take you off this study if you have serious side effects, or if your study doctor determines that it is no longer in your best interest to continue. The sponsor or regulatory agencies may stop this study at any time without your consent. Reasons why this might occur include you no longer meet eligibility criteria or noncompliance to study procedures or safety concerns. If this occurs, you will be notified, and your study doctor will discuss this with you. If the doctor determines you must not continue in the study, no new data about you will or blood and urine samples will be collected for study purposes unless the data concerns an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record. All data that have already been collected for study purposes, including the results of the analysis of your blood and urine, and any new information about an adverse event related to the study, will be sent to the study sponsor. Your blood and urine samples collected during the study will not be stored for future research and will

not result in any commercial profit. You will not be compensated for the use of your samples other than what is described in this consent form.

A description of this clinical trial will be available on https://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.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or a research-related injury, or if you have problems, concerns, questions or suggestions about the research, contact Dr. Jeffrey Guptill at 919-684-1672 during regular business hours and at 919-684-8111 after hours and on weekends and holidays.

For questions about your rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

STATEMENT OF CONSENT
"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form."

_____	_____	_____
Signature of Study Participant	Date	Time
_____	_____	_____
Signature of Person Obtaining Consent	Date	Time