Ketamine for Postoperative Avoidance of Depressive Symptoms: The K-PASS Feasibility Trial

Protocol Number: 2.0

National Clinical Trial (NCT) Identified Number: NCT05233566

Principal Investigator: Bradley A. Fritz, MD, MSCI

Funded by: Center for Perioperative Mental Health

Version Number: v.2.1

December 12, 2022

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
8.1	Post-operative MADRS assessments may be performed *approximately* on the specified days.	After hospital discharge, sometimes it is not possible to reach the patient by phone for a follow-up assessment on the specified day. When this happens, we would like to attempt to reach the patient on a subsequent day rather than leaving the data point as missing data.
8.1	Dreem data collection in preoperative holding has been added.	Because most patients are now providing consent via a telephone conversation and DocuSign rather than in person, the opportunity to send the patient home with a Dreem headband for preoperative data collection is no longer available. To identify preoperative electroencephalogram markers of treatment responsiveness, we would like to obtain a short period of electroencephalogram data collection in preoperative holding.

Table of Contents

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

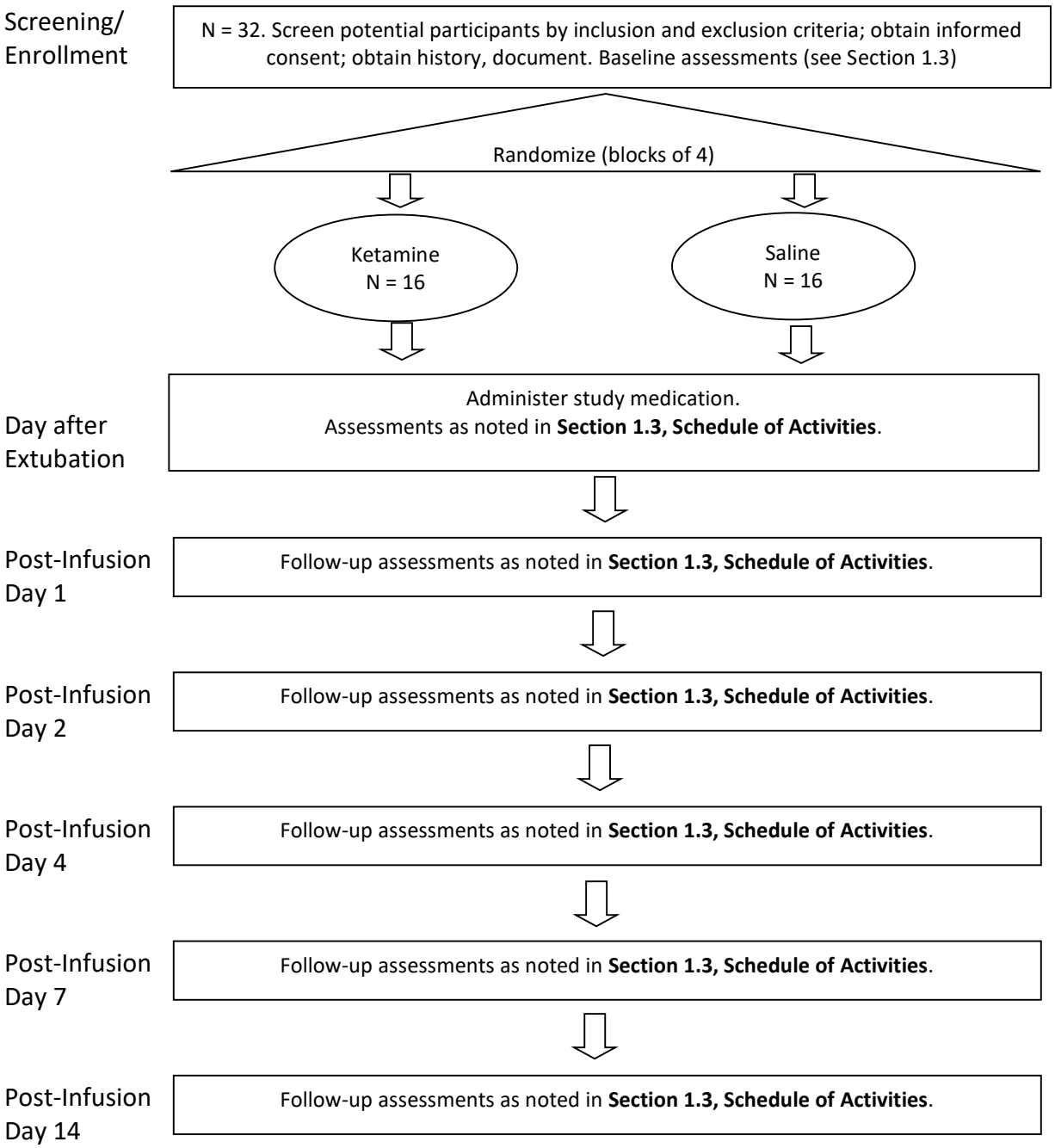
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Ketamine for Postoperative Avoidance of Depressive Symptoms: The K-PASS Feasibility Trial
Study Description:	This trial will evaluate the feasibility of conducting a larger placebo-controlled randomized clinical trial focused on the use of a postoperative, sustained low-dose ketamine infusion to reduce depressive symptoms.
Objectives:	Primary Objectives: 1. To evaluate the feasibility of recruiting participants to the randomized trial. 2. To evaluate the feasibility of delivering the study medication. 3. To evaluate the feasibility of collecting participant outcomes. Secondary Objectives: 1. To estimate the effect size for the difference in postoperative depressive symptoms between the intervention and control groups. 2. To estimate the effect size for the difference in delta sleep ratio between the intervention and control groups.
Endpoints:	Primary Endpoints: 1. Fraction of approached patients who enroll and are randomized 2. Fraction of randomized patients who complete the study medication infusion 3. Fraction of data points with successful capture of depressive symptom data and with successful capture of EEG data Secondary Endpoints:

	1. Change in Montgomery-Asberg Depression Rating Scale score between pre-operative time point and post-infusion day 4 2. Delta sleep ratio on electroencephalogram obtained postoperative day 1
Study Population:	Adult patients with past medical history of depression undergoing non-ambulatory surgery scheduled for at least 2 hours.
Phase:	3
Description of Sites/Facilities Enrolling Participants:	Single-center (Washington University in St. Louis School of Medicine)
Description of Study Intervention:	After extubation, patients in the intervention group will receive ketamine 0.5 mg/kg over 10 minutes followed by a sustained infusion at 0.3 mg/kg/h for an additional 2 hours 50 minutes.
Study Duration:	1 year
Participant Duration:	4 weeks

1.2 SCHEMA


Screening/ Enrollment
N = 32. Screen potential participants by inclusion and exclusion criteria; obtain informed consent; obtain history, document. Baseline assessments (see Section 1.3)
Randomize (blocks of 4)
Ketamine N = 16
Saline N = 16
Day after Extubation
Administer study medication.
Assessments as noted in **Section 1.3, Schedule of Activities**.
Post-Infusion Day 1
Follow-up assessments as noted in **Section 1.3, Schedule of Activities**.
Post-Infusion Day 2
Follow-up assessments as noted in **Section 1.3, Schedule of Activities**.
Post-Infusion Day 4
Follow-up assessments as noted in **Section 1.3, Schedule of Activities**.
Post-Infusion Day 7
Follow-up assessments as noted in **Section 1.3, Schedule of Activities**.
Post-Infusion Day 14
Follow-up assessments as noted in **Section 1.3, Schedule of Activities**.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening/Enrollment Day -7 to -1	Day of Surgery	Day of Extubation	Post-Infusion Day 1	Post-Infusion Day 2	Post-Infusion Day 4	Post-Infusion Day 7	Post-Infusion Day 14
Informed consent	X							
Demographics	X							
Medical history	X							
Alcohol Use Disorders Identification Test	X							
Drug Abuse Screening Test	X							
Childhood Trauma Questionnaire	X							
Montgomery-Asberg - Depression Rating Scale	X			X	X	X	X	X
Clinical Global Impression	X			X	X	X	X	X
Quick Inventory of Depressive Symptomatology	X			X	X	X	X	X
Pain assessment	X			X	X	X	X	X
DREEM device instructions	X							
EEG collection	X		X	X				
Retrieve DREEM device		X		X	X			
Randomization			X					
Administer study medication			X					
Brief Psychiatric Rating Scale four-item positive subscale			X					
Clinical Administered Dissociative State Scale			X					
Clinical and Adverse Events Checklist			X					X
Concomitant medication review	X	X	X	X	X	X	X	X
Adverse event review and evaluation	X	X	X	X	X	X	X	X
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

Depression is a disorder characterized primarily by depressed mood and loss of interest or pleasure, with additional symptoms such as changes in weight or appetite, slow thought or movement, fatigue, feelings of worthlessness or guilt, poor concentration, or suicidal ideation. Approximately 25-50% of patients presenting for surgery have a history of depression.[1-5] Patients with a history of preoperative depression are at elevated risk for experiencing depressive symptoms after surgery. In a cohort of 248 neurosurgical patients, lifetime history of depression was an independent predictor of postoperative depressive symptoms.[6] Similar results have been observed in cardiac surgery.[1] When scores on various depression scales are analyzed as continuous variables, higher preoperative scores have consistently

been significant predictors of higher postoperative scores.[7-9] Increased postoperative depressive symptoms have been linked to increased pain,[10] more frequent hospital readmissions within six months,[11] as well as increased mortality in short-term and long-term follow-up.[12]

Currently, prevention and treatment of postoperative depressive symptoms generally focuses on continuation, resumption, or initiation of oral antidepressants. For general treatment of depression in adults and older adults, the American Psychiatric Association recommends second-generation antidepressants such as selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors as first-line pharmacotherapy.[13] Following initiation or dose titration, these medications take several weeks to achieve their full effect,[14-16] limiting their effectiveness to prevent acute depressive symptoms after surgery. Furthermore, it may not be possible to give these medications in some instances due to impaired gastrointestinal absorption or motility or due to concern for medication interactions such as serotonin syndrome.

Ketamine is a promising prophylactic agent for postoperative depressive symptoms because it has shown efficacy for treatment-resistant depression and provides relief of depressive symptoms more rapidly than traditional biogenic amine-based antidepressants (e.g., selective serotonin reuptake inhibitors).

2.2 BACKGROUND

The NMDA receptor antagonist ketamine has shown promise as a novel, rapid-acting therapy for treatment-resistant depression. In 2006, Zarate and colleagues published an 18-patient randomized trial that demonstrated improved Hamilton Depression Rating Scale scores following 0.5 mg/kg ketamine infused over 40 minutes compared to placebo.[17] Since then, this finding has been replicated multiple times, with a recent meta-analysis of 19 studies reporting that a single infusion of ketamine led to improved depressive symptoms compared to placebo at 4 hours and 24 hours.[18] This is a much faster effect than oral antidepressants such as selective serotonin reuptake inhibitors, which take weeks to achieve maximum effect. Additional trials have demonstrated superiority of ketamine compared to active comparators such as midazolam.[19,20]

The antidepressant properties of ketamine are potentially mediated by a sequence of events that lead to synaptogenesis and increased electroencephalogram (EEG) slow wave activity (SWA). Ketamine administration results in increased extracellular glutamate in the prefrontal cortex,[21-23] initiating a chain of events[24,25] that leads to increased prefrontal synaptic density.[26] Enhanced synapse creation during wakefulness is followed by enhanced synapse pruning during subsequent sleep, which can be observed as SWA (1-4 Hz total EEG power) during non-rapid eye movement (NREM) sleep.[27] Low SWA during baseline sleep predicts ketamine responsiveness in depressed patients,[28] and increases in SWA following ketamine infusion correlate with symptom response.[29]

Although ketamine achieves its antidepressant effect rapidly, the effect of a single bolus wanes over the first week, and strategies to achieve longer effects have been explored. A common strategy has been to use repeated intravenous ketamine boluses administered two or three times per week,[30,31] although intranasal administration of the S enantiomer of ketamine has also been reported.[32-34] Symptoms can be controlled for multiple weeks, but ongoing therapy is needed to sustain the effect.[35] An alternative strategy that eliminates the need for repeated dosing is to use a long-duration of infusion. Pilot studies have demonstrated that a 96-hour ketamine infusion titrated to a goal of 0.6 mg/kg/h leads to a rapid

reduction in depressive symptoms that can be sustained in a large majority of responders for up to 8 weeks after the end of infusion.[36,37]

Lessons learned from treatment-resistant depression may guide the prevention of postoperative depressive symptoms. Ketamine is already familiar in this setting because it is sometimes used to provide sedation or to augment analgesia.[38,39] Boluses of 0.25-0.5 mg/kg during Cesarean section have been associated with either no effect[40] or with reductions in postpartum depression.[41,42] In surgery with general anesthesia, ketamine boluses near the time of induction have been associated with reduced postoperative depressive symptoms among patients with a history of depression[43,44] but not in a general population of older adults.[45] In those studies where a significant beneficial effect was observed, the effect quickly waned over the first few days after surgery. Treatment strategies that produce longer-lasting effects are desirable, but the longer-duration infusion that has shown promise in treatment-resistant depression has not been tested around the time of surgery.

Therefore, we hypothesize that a postoperative sustained, low-dose ketamine infusion can prevent postoperative depressive symptoms compared to placebo, when administered to a targeted population of surgical patients with a history of depression.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The risks associated with ketamine have been observed in studies evaluating its use for general anesthesia (as a sole agent, for induction, or as a supplement to other agents), which general involve higher doses than those to be used in this study.[46]

Immediate risk of ketamine use may include

- Hypertension and tachycardia – These are common events at higher doses. Ketamine is contraindicated in patients for whom a significant elevation of blood pressure would constitute a serious hazard. (Of note, the low doses to be used in this study have not previously been associated with clinically significant changes in blood pressure or heart rate.[36])
- Psychotomimetic effects – These have occurred in approximately 12% of patients following anesthetic doses. These may range from pleasant dream-like states to vivid imagery, hallucinations, and emergence delirium.
- Respiratory depression – This is an uncommon event and may occur with overdosage or too rapid a rate of administration.
- Nystagmus, diplopia – These are common events. Rarely these may be associated with increases in intraocular pressure.
- Enhanced skeletal muscle tone
- Anorexia, nausea, vomiting
- Anaphylaxis

Long-range risks of ketamine include

- Pediatric neurotoxicity - Animal studies demonstrate increased neuronal apoptosis in developing juvenile brains and long-term cognitive deficits when used for longer than 3 hours.

2.3.2 KNOWN POTENTIAL BENEFITS

Participants may experience direct benefits from participation in this study. These benefits are described below.

Reduced Incidence of Depressive Symptoms – As described in section 2.2, ketamine has been used successfully to improve symptoms in patients with treatment-resistant depression. Boluses of ketamine have been associated with reduced incidence of postpartum depression and transient reductions in depressive symptoms following general anesthesia. Patients in this study may experience reduced incidence of depressive symptoms following surgery if randomized to the intervention group.

Analgesia – Patients who receive ketamine may benefit from improved pain control. In a 2018 Cochrane meta-analysis including 8,341 patients from 130 studies who underwent surgery with general anesthesia, ketamine was associated with improved pain scores at rest and with movement at 24 hours and 48 hours postoperatively.[38] Patients who received ketamine also had reduced opioid consumption at 24 hours and 48 hours.[38] Lower pain scores and decreased opioid consumption were similarly reported in a meta-analysis of 1,737 patients from 20 trials examining the effect of ketamine on pain following Cesarean section.[39]

In addition to the direct benefits to patients, there will be benefits to society. When successfully completed, this line of research will yield knowledge about whether a postoperative ketamine infusion can prevent or mitigate subsequent depression. Investigation of concurrent EEG markers may also yield insights regarding the effects of ketamine infusion on sleep architecture and potential mechanistic associations between sleep architecture and postoperative depressive symptoms. This knowledge will benefit future patients by informing treatment decisions that will enhance mental health following surgery.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

We have taken steps to reduce the potential risks to the fullest extent possible. By using a lower dose of ketamine than is commonly used for general anesthesia and by using a dosing protocol that avoids rapid boluses, we reduce the likelihood of hypertension, tachycardia, psychotomimetic effects, and respiratory depression. Furthermore, we reduce the risks associated with hypertension by excluding patients for whom a significant elevation of blood pressure would constitute a serious hazard. We reduced the likelihood of pediatric neurotoxicity by excluding pregnant patients and by excluding subjects less than 18 years of age. By conducting a small feasibility study prior embarking on a larger randomized clinical trial, we will maximize our ability to test the primary hypothesis and generate knowledge that will benefit society. Given these facts, we feel the benefits to patients and to society outweigh the risks associated with this study.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To evaluate the feasibility of recruiting participants to the randomized trial.	Fraction of patients approached who enroll and are randomized.	This endpoint provides an evaluation of how long it would take to

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		complete enrollment in a full-scale clinical trial.
To evaluate the feasibility of delivering the study medication.	Fraction of randomized patients who complete the study medication infusion.	This endpoint provides an evaluation of whether infusions were missed for logistical reasons and whether infusions were stopped early due to side effects.
To evaluate the feasibility of collecting participant outcomes.	Fraction of randomized patients with Montgomery-Asberg Depression Rating Scale (MADRS) scores available at all specified time points.	This endpoint provides an evaluation of whether the primary outcome for the full-scale clinical trial can be measured.
Secondary		
To estimate the effect size for the difference in postoperative depressive symptoms between patients receiving ketamine and patients receiving placebo.	Change in MADRS score between the preoperative assessment and post-infusion day 4	The MADRS is a reliable, valid measurement tool for depressive symptoms.
To estimate the effect size for the difference in delta sleep ratio between the intervention and control groups.	Delta sleep ratio on EEG obtained on post-infusion night 1	The delta sleep ratio, defined as the ratio between 1-4 Hz SWA during the first and second non-rapid eye movement epochs during sleep, has previously been associated with ketamine responsiveness.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The primary hypothesis underlying this work is that a postoperative sustained, low-dose ketamine infusion can prevent postoperative depressive symptoms when administered to a targeted population of surgical patients with a history of depression.

This protocol describes a feasibility trial that will evaluate the feasibility of conducting a full-scale phase 3 trial. Both the feasibility trial and the full-scale trial will follow a randomized, placebo-controlled,

double-blinded, parallel design. The trial will follow a superiority design. This trial will take place at a single site (Washington University in St. Louis School of Medicine/Barnes-Jewish Hospital).

Following extubation, patients will be randomized to the intervention (ketamine group) or to control (control group). Patients in the ketamine group will receive a bolus of ketamine 0.5 mg/kg intravenously over 10 minutes, followed by an infusion at 0.3 mg/kg/h for an additional 2 hours 50 minutes. Patients in the control group will receive an equal volume of normal saline. Additional details about dosing and administration are found in section 6.1.2. Patients, research staff performing assessments, and research staff performing data analysis will be blinded to treatment allocation.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A saline placebo has been selected for the control group because the study intervention (ketamine) represents an addition to the usual postoperative care plan rather than a replacement for an existing therapy. One potential problem with this choice of control is that patients in the ketamine group may be able to guess their treatment allocation if they experience side effects such as hallucinations or diplopia. To assess for the presence of this problem, we will ask patients to guess which treatment they received. Despite this potential problem, a saline placebo remains preferable to an active placebo such as a benzodiazepine because it is a better approximation of current usual care.

4.3 JUSTIFICATION FOR DOSE

In the intervention group, the dosing regimen has been designed to quickly achieve the desired blood level of ketamine of 225 ng/mL and then maintain that level throughout the infusion. A desired blood level of 225 ng/mL has been selected because this is half of the serum concentration obtained during steady state for a 96-hour infusion.[36] This level is also only slightly higher than the peak blood level obtained after patients receive a 0.5 mg/kg bolus dose delivered over 40 minutes, first described by Krystal in 1994[47] and used frequently in subsequent studies. Such a dosing approach would address the question of clinical utility in prolonging the length of anticipated NMDA receptor blockade from several minutes to 8 hours.

Loading Dose – The alpha distribution half-life for ketamine is about 10 minutes. A load over 10 minutes instead of an immediate bolus should be feasible in that this would lessen the likelihood of significant sedation, and it would provide time to detect the rare instances of more moderate sedation with the load. Thus, this loading approach carries minimal risk of unintended over-sedation. Also given the beta half-life of about 2.3 hours, there would not be substantial loss of ketamine during the 10-minute load.

The risk of over-sedation may be larger in patients with elevated body mass index (BMI), due to a higher peak concentration prior to redistribution throughout all tissue (including the excess adipose). To reduce the peak concentration without decreasing the expected plasma concentration at the end of the bolus load, the bolus load duration will be increased to 20 minutes in patient with BMI > 40.

We want to load the patient with an amount equal to 100% of the desired steady state. Thus, the loading dose is equal to the product of the volume of distribution and the desired plasma concentration. Per Wagner and O'Hara,[48] the volume of distribution of ketamine is 2.4 L/kg. As noted above, the desired plasma concentration is 225 ng/mL, which is equal to 0.225 mg/L. Therefore, the loading dose will be

$$2.4\frac{\text{L}}{\text{kg}} \times 0.225\frac{\text{mg}}{\text{L}} = 0.54\frac{\text{mg}}{\text{kg}}$$

Thus, we will plan to load with a bolus of 0.5 mg/kg over 10 minutes (or over 20 minutes if BMI > 40).

Infusion Dose – In a previous study of 23 patients with treatment-resistant depression who received a 96-hour infusion of intravenous ketamine, serum ketamine levels were directly measured.[37] An infusion of 0.6 mg/kg/h produced a steady-state blood level of about 450 ng/mL. Therefore, an infusion at half that rate (0.3 mg/kg/h) would be expected to produce a 50% lower steady-state blood level of 225 ng/mL.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Able to provide written, informed consent
2. Aged 18 or older
3. Scheduled for non-ambulatory surgery scheduled to last at least 2 hours at Barnes-Jewish Hospital
4. Past medical history of depression, defined as one or more of the following criteria
    a. Previous diagnosis by a psychiatrist or primary care physician in an outpatient or inpatient setting, by patient report or chart documentation
    b. Prescription of an oral antidepressant by a psychiatrist or primary care physician for a mood disorder

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Bipolar depression
2. Concurrent use of a medication contraindicated with ketamine
3. Emergent surgery
4. Known or suspected elevation in intracranial pressure
5. Current subarachnoid hemorrhage
6. Carotid endarterectomy or arteriovenous malformation repair
7. Allergy to ketamine
8. Any condition in which a significant elevation of blood pressure would constitute a serious hazard (e.g., aortic dissection, pheochromocytoma)
9. Known history of dementia
10. Pregnancy or lactation
11. Inability to converse in English

12. Concurrent enrollment in another interventional trial

Comorbid anxiety and outpatient anxiolytic use will be neither inclusion criteria nor exclusion criteria.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Examples of situations that may result in screen failure include patient death, surgery cancellation, and postoperative mechanical ventilation for > 72 hours. In the case of surgery cancellation, the patient may be rescreened if they are scheduled for another surgery during the trial period.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Anticipated Patient Population – The target sample size will be 32 patients. Patients will be enrolled at a single site (BJH/Washington University School of Medicine). The expected accrual rate was estimated by examining characteristics (obtained via Epic Slicer Dicer at the population level only) of a retrospective cohort of patients who had non-emergent surgery at BJH between 1/1/2021 and 6/30/2021, had an ICU admission, and had an ICD grouper corresponding to depression documented in the diagnosis list or the past medical history. The query was limited to the cardiac, neurosurgery, and vascular services because many of the patients from other services (e.g., trauma, orthopedic) were suspected to have initially had emergent surgery followed by an ICU admission and then a non-emergent surgery. Exclusion criteria for the retrospective query included age < 18. During that 6-month time period, there were 307 patients who met these criteria (Figure 2). If we conservatively estimate that 20% of these patients enroll in the trial, that results in an accrual of 10 patients per month.

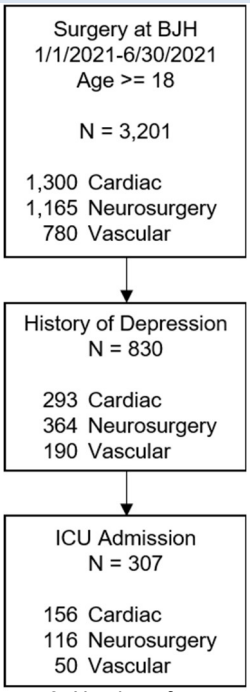


Figure 2. Number of potentially eligible patients in a 6-month period.

The gender, race and ethnicity, and age distributions are expected to follow the gender, race and ethnicity, and age distributions served by the Barnes-Jewish Hospital. These distributions were observed in the retrospective cohort seen in Figure 2. The anticipated characteristics of the study population are shown in Table 1.

Table 1. Anticipated Demographic Characteristics of the Study Population

Racial Categories	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	

American Indian/ Alaska Native	1	0	0	0	1
Asian	1	0	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	2	0	0	4
White	13	11	1	1	26
More than One Race	0	0	0	0	0
Total	17	13	1	1	32

Recruitment Strategy – Patients will primarily be recruited at the Center for Preoperative Assessment and Planning (CPAP). Potentially eligible patients will be identified by screening the CPAP schedule. Patients identified via screening will be approached by telephone prior to their CPAP appointment or in person at CPAP.

In addition, the operating room schedule will be reviewed to identify potentially eligible patients admitted to the hospital before surgery who did not visit CPAP. These patients will be approached in person in the hospital prior to the day of surgery.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The study intervention is ketamine. Per the package insert, "Ketamine is a nonbarbiturate general anesthetic chemically designated *dl* 2-(0-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride. It is formulated as a slightly acid (pH 3.5-5.5) sterile solution for intravenous or intramuscular injection in concentrations containing the equivalent of either 10, 50, or 100 mg ketamine base per milliliter and contains not more than 0.1 mg/mL Phemerol® (benzethonium chloride) added as a preservative. The 10 mg/mL solution has been made isotonic with sodium chloride."[46]

Ketamine is indicated as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation, for the induction of anesthesia prior to the administration of other general anesthetic agents, and for supplementation of low-potency agents such as nitrous oxide.[46] It is frequently used off-label for other purposes such as sedation in the intensive care unit and for analgesia.

This trial involves use of an FDA-approved drug for a purpose not listed on the package insert. This trial is exempt from IND requirements because it meets all the criteria in CRF 312.2(b):

- The investigation is not intended to be reported to the FDA to support a new indication or to change the drug labeling.
- The drug is lawfully marketed in the United States as a prescription drug product.
- The investigation does not involve a route of administration, a dosage level, or a patient population that significantly increases the risks compared to the labeled indication.
- The investigation complies with the requirements for IRB review and informed consent.
- The investigation is not intended to promote or commercialize the drug product.

6.1.2 DOSING AND ADMINISTRATION

The study intervention consists of a bolus loading dose followed by a continuous infusion. For patients in the intervention group, the bolus loading dose will consist of ketamine 0.5 mg/kg administered intravenously over 10 minutes (or over 20 minutes if BMI > 40). This will be followed by a continuous infusion at 0.3 mg/kg/h for an additional 2 hours 50 minutes.

Patients in the control group will receive an equal volume of normal saline. The bolus loading dose will consist of normal saline 0.1 mL/kg administered intravenously over 10 minutes (or over 20 minutes if BMI > 40). This will be followed by a continuous infusion at 0.06 mL/kg/h for an additional 2 hours 50 minutes.

Study intervention dosing will be based on actual body weight.

Timing of study medication administration will be the same for both groups. For patients who are extubated in the operating room, the study medication will be initiated prior to leaving the operating room. For patients who remain intubated and transfer to the intensive care unit, the study medication will be administered based on the following criteria:

- If the patient is extubated before 07:00am on postoperative day 1, the study medication will be administered between 05:00am and 08:00am on postoperative day 1.
- If the patient is extubated after 07:00am on postoperative day 1 and before 07:00am on postoperative day 2, the study medication will be administered between 05:00am and 08:00am on postoperative day 2.
- If the patient is extubated after 07:00am on postoperative day 2 and before 07:00am on postoperative day 3, the study medication will be administered between 05:00am and 08:00am on postoperative day 3.
- If the patient remains intubated at 07:00am on postoperative day 3, the patient will be withdrawn from the study.

In the operating room, the study medication will be administered by the anesthesiology clinician (MD or certified registered nurse anesthetist). In the PACU or ICU, the study medication will be administered by the patient's bedside nurse.

Richmond Agitation and Sedation Scale (RASS) scores will be monitored per standard nursing protocols, as described in section 8.2. If the patient experiences sedation to a RASS score ≤ -2, then the study medication will be halted and the procedures documented in section 7.1 will be followed.

If the RASS score is ≤ -2 before initiation of the study medication, then the study medication will not be initiated at that time. The patient will be re-evaluated the following day, and the study medication will be initiated when the RASS is no longer ≤ -2. If RASS remains ≤ -2 on postoperative day 3, the patient will be withdrawn from the study.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Ketamine will be purchased in multidose vials through the BJH Investigational Drug Service. The study medication (ketamine or normal saline) will be prepared by the Investigational Drug Service after an order has been placed in Epic by the research team. The study medication will be delivered to the

patient's bedside nurse by the Investigational Drug Service utilizing a controlled substance chain of custody form. Any unused study medication will be returned to the Investigational Drug Service and destruction of unused ketamine will be done in accordance with federal, state, and institutional regulations.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Ketamine hydrochloride is a 50 mg/mL sterile solution that is clear, colorless, and free of visible particles. It will be purchased in multidose vials containing 500 mg in 10 mL. Ketamine will be manufactured by PAR Pharmaceuticals.

Normal saline is a sterile, preservative free solution that is clear, colorless, and free of visible particles. It will be manufactured by Baxter Healthcare.

6.2.3 PRODUCT STORAGE AND STABILITY

Per the package insert, ketamine is to be stored at a temperature between 20°C and 25°C (68°F to 77°F) and is to be protected from light.[46] The product will be stored by BJH Investigational Drug Service in a secure location under proper & monitored environmental conditions.

Each multi-dose vial has a beyond-use date of 28 days after initial use.

6.2.4 PREPARATION

Medication preparation will be performed by the BJH Investigational Drug Service using proper aseptic technique in accordance with USP Chapter 797. Ketamine will be diluted using normal saline to a concentration of 5 mg/mL (e.g., 500 mg in 100 mL). Both ketamine and normal saline placebo will be delivered in 100 mL bags that have identical appearance except for a unique study identifier.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization will occur postoperatively at the time of study medication preparation. Patients will be randomized in a 1:1 ratio to ketamine or normal saline placebo. Randomization will occur in blocks of 4. The randomization scheme will be held by the Investigational Drug Service.

Patients, research team members, and clinical staff (nurses, physicians) will be blinded to treatment allocation. To facilitate blinding, study medication for both the ketamine group and the control group will be delivered in 100 mL bags with identical appearance except for a unique study identifier.

Intentional unblinding of the clinical staff may occur in the case of serious adverse events if the attending physician feels knowledge of the treatment allocation will impact clinical decision making. The principal investigator will be notified of all instances of intentional unblinding.

Inadvertent unblinding may occur if the patient experiences side effects such as nystagmus, hallucinations, sedation, or hypertension/tachycardia. To detect inadvertent unblinding of the patient, we will ask the patient during the final study visit if they believe they received ketamine or placebo. To minimize the effects of inadvertent unblinding on study results, endpoints will be measured by study staff who were not present during the study medication infusion.

6.4 STUDY INTERVENTION COMPLIANCE

Because the study medication will be ordered in Epic and administered by the clinical bedside nurse, medication administration will be documented in Epic per usual nursing policies. Compliance will be assessed via review of the electronic health record documentation.

6.5 CONCOMITANT THERAPY

Intraoperatively, enrolled participants should not receive open-label ketamine. Otherwise, all components of the anesthetic care plan will be at the discretion of the attending anesthesiologist.

Postoperatively, enrolled participants should not receive open-label ketamine. During the study medication infusion, concurrent infusions of propofol, midazolam, or other sedative agents with GABA receptor activity will not be permitted. Concurrent dexmedetomidine is permitted. During the study medication infusion, administration of benzodiazepines or gabapentin will not be permitted. All other components of postoperative care will occur as directed by the clinical team.

Medications administered to the patient will be retrieved by the research team from the electronic health record. In particular, administrations of the following medication classes between 05:00am on the day of the study medication infusion and 06:00am on post-infusion day 2 will be retrieved:

- Benzodiazepines
- Anticonvulsants
- Alpha agonists (dexmedetomidine, clonidine)
- Hypnotic agents
- Antihypertensive agents
- Antiarrhythmic agents

Administrations of the following medication classes between 06:00am on the day of the study medication infusion and 06:00am on post-infusion day 7 will be retrieved:

- Opioid analgesics
- Non-opioid analgesics
- Antiemetics

6.5.1 RESCUE MEDICINE

Not applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Infusion of the study medication may be halted if the patient experiences sedation to a Richmond Agitation and Sedation Scale (RASS) score of -2 (light sedation: briefly awakens <10 sec with eye contact to voice) or lower. Once the patient has returned to a RASS of -1 (drowsy: sustained awakening >10 sec with eye contact to voice) or greater, the study medication may be restarted as noted below:

- If the medication was halted during the bolus loading dose, then the bolus will not be resumed. After recovery to RASS ≥ -1, the continuous infusion will be started at 0.3 mg/kg/h ketamine or 0.06 mL/kg/h normal saline.

- If the medication was halted during the continuous infusion of 0.3 mg/kg/h ketamine or 0.06 mL/kg/h normal saline, then the infusion will be restarted at 0.2 mg/kg/h ketamine or 0.04 mL/kg/h normal saline after recovery to RASS ≥ -1.
- If the medication was halted during an infusion at 0.2 mg/kg/h ketamine or 0.04 mL/kg/h normal saline, then the infusion will be restarted at 0.15 mg/kg/h ketamine or 0.03 mL/kg/h normal saline after recovery to RASS ≥ -1.
- If the medication was halted during an infusion at 0.15 mg/kg/h ketamine or 0.03 mL/kg/h normal saline, then the infusion will not be restarted.

Discontinuation of the study medication as described in this section may result in inadvertent unblinding of the patient and clinical staff. We will assess for inadvertent unblinding as described in section 6.3.

If 3 patients require the study medication to be halted, then the principal investigator will consider revising the dosages and/or infusion rates listed in section 6.1.2.

If the clinical team feels it is necessary to halt the study medication for a reason other than RASS < -1, this will be discussed with the principal investigator or a qualified designee.

Discontinuation of the study medication does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she is unable to be contacted by the study site staff after hospital discharge for three consecutive follow-up assessments.

For each post-discharge follow-up assessment, the following actions will be taken if the patient is unable to be contacted:

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Depressive Symptom Measurement

Depressive symptoms will be measured using the Montgomery-Asberg Depression Rating Scale (MADRS) preoperatively and on post-infusion days 1, 2, 4, 7, and 14. The MADRS rates the severity of 10 depressive symptoms based on a targeted clinical interview, yielding a total score 0 (no symptoms) and 60 (severe symptoms).[49,50] The scale has been found to correlate highly with a global clinician assessment (Pearson correlation = 0.71)[51] and to have high inter-rater reliability.[49] The MADRS has been modified to assess symptoms over the previous day rather than the previous week.[36,37] This modified version will be used on the post-infusion days.

The MADRS will be administered by a trained research team member. Post-infusion assessments will be conducted between 07:00am and 12:00pm approximately on the specified days. The time of day for the preoperative assessment will be variable, depending on the time of the patient's CPAP appointment or in-hospital visit. If the patient is discharged from the hospital before the day of the final study assessment, the MADRS will be conducted over the telephone.

Concurrent with each MADRS assessment, the research team member will use the Clinical Global Impression (CGI) to rate the overall severity of the patient's mental illness.[52] At each postoperative follow-up, the CGI will also be used to rate the overall level of improvement compared to the previous assessment.
Concurrent with each MADRS assessment, self-reported depressive symptoms will be collected using the Quick Inventory of Depressive Symptomatology (QIDS).[53]

The MADRS includes questions about suicidal ideation. If the patient reports any suicidal ideation, then the Suicide Risk Management Protocol will be initiated. This includes a structured assessment allowing stratification of the risk for self-harm, notification of the principal investigator, and (if risk is moderate or high) notification of an on-call psychiatrist.

Electroencephalogram (EEG) Measurement

EEG will be captured using the Dreem headband (DREEM, Rhythm, New York, NY), a consumer-grade wireless device using dry electrodes. The device uses five EEG channels (F7, F8, FpZ, O1, O2), accelerometry, and pulse oximetry. It samples EEG electrode potentials at a rate of 250 Hz and applies a 0.4-30 Hz bandpass filter.

At the baseline visit, the research team member will teach the participant how to use the Dreem headband for data collection. If the participant is recruited in the CPAP clinic, then the participant will take the Dreem headband home with them. They will be instructed to wear the headband and activate data collection while sleeping for one night. They will bring the headband back to the hospital with them

on the day of surgery. If the participant is recruited in the hospital, then the participant will wear the headband and activate data collection while sleeping the night following enrollment. The headband will be retrieved the following day.

Additional data collection using the Dreem headband will occur in preoperative holding, during the study medication infusion, the night following the study medication infusion, and the night following post-infusion day 1.

Postoperative Pain

Pain will be measured at the baseline visit and on post-infusion days 1, 2, 4, 7, and 14 using the visual analog scale. The participant will rate their pain at rest, when taking a deep breath, and with movement.

If the participant is discharged from the hospital before the day of the final study assessment, pain will be assessed over the telephone using an 11-point numeric rating scale at each remaining study time point. Pain will be rated at rest, when taking a deep breath, and with movement.

Postoperative Delirium

Delirium is assessed routinely by the ICU nurses using the Confusion Assessment Method for the ICU (CAM-ICU) once per shift. CAM-ICU scores between the day of the infusion and post-infusion day 5 will be retrieved from the electronic health record.

8.2 SAFETY AND OTHER ASSESSMENTS

Psychotomimetic Side Effects

Psychotomimetic effects will be quantified using the Brief Psychiatric Rating Scale (BPRS) four-item positive symptom subscale[36,54] and using the modified 6-item Clinical Administered Dissociative State Scale (CADSS-6).[55] The BPRS four-item subscale yields a score between 4 (no symptoms) and 28 (extremely severe). The CADSS-6 yields a score between 0 (no symptoms) and 24 (severe symptoms). Both scales will be administered by a research team member midway through the study medication infusion (approximately 1-2 hours after the start of the bolus loading dose).

Clinical and Adverse Events Checklist

Additional side effects of ketamine will be detected using the Clinical and Adverse Events Checklist.[56] This checklist will be administered by a research team member midway through the study medication infusion (approximately 1-2 hours after the start of the bolus loading dose). The checklist will be repeated on post-infusion day 14 to monitor for resolution of any side effects.

Level of Sedation

Although the doses of ketamine used in this study are not expected to produce clinically significant sedation, patients will be monitored for sedation using the Richmond Agitation and Sedation Scale (RASS). RASS assessments will be conducted by the clinical bedside nurse per standard nursing protocols of the ICU. The nurse will also be asked to perform one extra RASS assessment at the end of the 10-minute bolus loading dose. If the RASS score is ever -2 or lower, the study medication will be held according to the protocol described in section 7.1.

Vital Signs during Study Medication Infusion

During the infusion, participants will receive vital sign monitoring per intensive care unit standard of care. This will include continuous telemetry, continuous pulse oximetry, and either intermittent

noninvasive blood pressure (at least hourly) or continuous invasive blood pressure (if an arterial catheter is present). Vital signs will be documented in the electronic health record by the clinical bedside nurse per unit standard of care. The research team will retrieve vital signs from the electronic health record.

Safety events will include significant hypertension during the infusion, defined as systolic blood pressure > 180 mmHg or the administration of an antihypertensive medication that is not one of the patient's home medications. Another safety event will be tachycardia, defined as heart rate > 100 beats per minute, during the infusion.

Nausea and Vomiting

At each post-infusion study visit, participants will be asked if they have experienced nausea or vomiting in the past 24 hours. If present, the patient will be asked to classify the event as mild, moderate, or severe. In addition, the electronic medical record will be reviewed for administration of antiemetic medication.

Baseline Factors Potentially Related to Depression

At the time of enrollment, the patient will complete several surveys evaluating factors that may be related to their depressive history or that may predict treatment responsiveness. These surveys will include the Generalized Anxiety Disorder 7-item scale (GAD-7),[57] the Alcohol Use Disorders Identification Test (AUDIT),[58] the Drug Abuse Screening Test (DAST-10),[59] and the Childhood Trauma Questionnaire (CTQ).[60]

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

The principal investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The principal investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Adverse events will be reported to the Washington University IRB according to the timeframes set forth by the IRB:

- An event that meets the definition of an unanticipated problem involving risk to participants or others and results in the death of a participant: will be reported within 1 working day.
- An event that meets the definition of an unanticipated problem involving risk to participants or others and does NOT result in the death of a participant: will be reported within 10 working days.
- Adverse events and serious adverse events that do not also meet the definition of an unanticipated problem involving risks to participants or others: will be reported annually during continuing review.
- An unexpected adverse drug event that result in the death of a participant: will be reported within 1 working day.
- An unexpected adverse drug events that does NOT result in the death of a participant: will be reported within 10 working days.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Individual participants will be notified of any serious, unanticipated adverse events probably related to study interventions.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable

8.3.9 REPORTING OF PREGNANCY

Not applicable

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;

- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs involving risk to participants or others and results in the death of a participant will be reported to the IRB within 1 working day.
- UPs involving risk to participants or others and does NOT result in the death of a participant will be reported to the IRB within 10 working days.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Participants will be informed of UPs if/when recommended by the IRB.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary endpoints of this trial will be descriptive outcomes measuring feasibility rather than hypothesis-driven efficacy outcomes. The primary endpoints will include

- Primary Endpoint 1: Fraction of approached patients who enroll in the trial
- Primary Endpoint 2: Fraction of planned study medication infusions that are completed
- Primary Endpoint 3: Fraction of participants with MADRS scores available at all specified time points

The secondary endpoints of this trial will be efficacy outcomes, designed to test the following hypotheses with two-sided superiority comparisons. This feasibility trial is intended to provide estimates of effect sizes, but it will not be powered to test these hypotheses.

- Secondary Endpoint 1: Change in MADRS score between the preoperative assessment and post-infusion day 4
    - Null Hypothesis: The change in MADRS score will be the same in the ketamine group and in the control group.
    - Alternative Hypothesis: The change in MADRS score will be smaller in the ketamine group than in the control group.
- Secondary Endpoint 1: Delta sleep ratio on EEG obtained on the second night following the study medication infusion
    - Null Hypothesis: There will be no difference in delta sleep ratio between the ketamine group and the control group.
    - Alternative Hypothesis: The delta sleep ratio will be greater in the ketamine group compared to the control group.

9.2 SAMPLE SIZE DETERMINATION

The sample size of 32 has been selected to allow the primary descriptive endpoints to be measured with acceptable levels of precision:

- Primary Endpoint 1: Fraction of approached patients who enroll in the trial

- Conservatively assuming that 25% of approached patients will enroll, then n = 32 patients will allow this proportion to be measured with a 95% confidence interval width of ±15%:

$$95\%\text{CI} = \pm 1.96\sqrt{\frac{p(1-p)}{n}} = \pm 1.96\sqrt{\frac{(0.25)(0.75)}{32}} = \pm 0.15$$

- Primary Endpoint 2: Fraction of planned study medication infusions that are completed
  - If we assume that 90% of planned infusions are completed, then n = 32 patients will allow this proportion to be measured with a 95% confidence interval width of ± 10%:

$$95\%\text{CI} = \pm 1.96\sqrt{\frac{p(1-p)}{n}} = \pm 1.96\sqrt{\frac{(0.90)(0.10)}{32}} = \pm 0.10$$

- Primary Endpoint 3: Fraction of participants with MADRS scores available at all specified time points
  - If we assume that 95% of participants will have scores available at all specified time points, then n = 32 patients will allow this proportion to be measured with a 95% confidence interval width of ± 7%:

$$95\%\text{CI} = \pm 1.96\sqrt{\frac{p(1-p)}{n}} = \pm 1.96\sqrt{\frac{(0.95)(0.05)}{32}} = \pm 0.07$$

This sample size does not provide power to test the secondary endpoints for superiority. However, the observed values will be used to determine effect sizes, as well as standard deviations for the observed values. These quantities will inform the sample size calculation for the full-scale clinical trial. A minimum of 24-30 patients has previously been recommended for estimating effects sizes,[61,62] so this feasibility trial should be large enough to provide the necessary estimates.

9.3 POPULATIONS FOR ANALYSES

The population for Primary Endpoint 1 will include all patients who are approached for enrollment in the trial. Primary Endpoints 2 and 3 will be analyzed in an intention-to-treat population that includes all patients who are randomized. The secondary endpoints will also be analyzed in the intention-to-treat population of all patients who are randomized.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

For descriptive statistics, categorical data will be presented using frequency counts and percentages, normally distributed continuous data will be presented using means and standard deviations, and non-normally distributed continuous data will be presented using medians and interquartile ranges. Normality will be assessed using visual analysis of histograms and using the Kolmogorov-Smirnoff test. All inferential tests will be two-tailed, and p-values < 0.05 will be considered statistically significant.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Primary Endpoint 1:

The fraction of approached patients who enroll in the trial will be described using a proportion. A 95% confidence interval will be used to present uncertainty around this proportion.

The numerator will include all participants who are randomized to receive either ketamine or the placebo.

The denominator will include all patients who are approached by the research team to evaluate eligibility and offer consent. This will include patients approached by telephone in advance of their CPAP appointment, patients approached in person at CPAP, and patients approached in person in the hospital prior to the day of surgery.

Primary Endpoint 2:
The fraction of randomized participants who complete the study medication infusion will be described using a proportion. A 95% confidence interval will be used to present uncertainty around this proportion.

The numerator will include all participants who receive the study medication for at least 7 of the planned 8 hours (if enrolled under protocol version 1) or for at least 2 of the planned 3 hours (if enrolled under protocol version 2). If the study medication is temporarily halted but later restarted, the participant will still be included in the numerator if the total time with an active infusion is above the threshold defined above.

The denominator will include all participants who are randomized to receive either ketamine or the placebo.

Primary Endpoint 3:
The fraction of participants with MADRS scores available at all the specified time points will be described using a proportion. A 95% confidence interval will be used to present uncertainty around this proportion.

The numerator will include all participants with MADRS scores documented at all of the following time points: preoperative baseline, post-infusion days 1, 2, 4, 7, and 14.

The denominator will include all participants who are randomized to receive either ketamine or the placebo.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary Endpoint 1:
For each randomized participant, the difference in MADRS score on post-infusion day 4 and at the preoperative baseline visit will be calculated. Participants with missing MADRS scores at either time point will be excluded. (No imputation of MADRS scores will be performed.)

The distribution of delta MADRS scores in the population will be assessed for normality using visual analysis of histograms and using the Kolmogorov-Smirnoff test. If the delta MADRS scores are normally distributed, then the mean delta scores in the two groups will be compared using a two-sample t-test. If the delta MADRS scores are not normally distributed, then the median delta scores in the two groups will be compared using a Wilcoxon rank sum test.

Secondary Endpoint 2:
For each randomized participant, the EEG collected on the second night following the study medication infusion will be analyzed by an experienced sleep technician to identify sleep stages. Within each time

epoch captured, slow wave activity will be defined as the total power in the 1-4 Hz frequency band. The delta sleep ratio (DSR) will be defined as the ratio of SWA during the first non-rapid eye movement (NREM) epoch to SWA during the second NREM epoch.

The distribution of DSRs in the population will be assessed for normality using visual analysis of histograms and using the Kolmogorov-Smirnoff test. If the DSRs are normally distributed, then the mean DSR in the two groups will be compared using a two-sample t-test. If the DSRs are not normally distributed, then the median DSR in the two groups will be compared using a Wilcoxon rank sum test.

9.4.4 SAFETY ANALYSES

Psychotomimetic Symptoms:
The BPRS four-item positive symptom subscale score and the CADSS-6 score will be calculated for each patient. The distribution of scores will be assessed for normality using visual analysis of histograms and using the Kolmogorov-Smirnoff test. If the scores are normally distributed, then the mean score in the two groups will be compared using a two-sample t-test. If the scores are not normally distributed, then the median score in the two groups will be compared using a Wilcoxon rank sum test.

Clinical and Adverse Events Checklist:
The number of patients reporting each side effect during the study medication infusion will be determined. The incidence of each side effect will be compared between the two groups using a chi-square test (or using a Fisher exact test in the case of rare side effects).

Significant Hypertension during Infusion:
The number of patients experiencing a systolic blood pressure > 180 mmHg during the study medication infusion or receiving an antihypertensive medication during the infusion that is not on the patient's home medication list will be determined. The incidence of significant hypertension will be compared between the two groups using a chi-square test.

Tachycardia during Infusion:
The number of patients experiencing a heart rate > 100 beats per minute during the study medication infusion will be determined. The incidence of tachycardia will be compared between the two groups using a chi-square test.

Nausea and Vomiting:
The number of patients reporting nausea and vomiting will be determined. The incidence of nausea and vomiting will be compared between the two groups using a chi-square test.

Other adverse events will be coded and reported as described in section 8.3.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline descriptive statistics will include demographic characteristics, past medical history including previous psychiatric diagnoses, preoperative use of psychoactive medications, and type of surgery planned. Descriptive statistics will be stratified by randomization allocation, but no inferential statistics will be used.

9.4.6 PLANNED INTERIM ANALYSES

No interim analyses are planned.

9.4.7 SUB-GROUP ANALYSES

The primary feasibility endpoints will also be assessed in sub-groups corresponding to surgical service (e.g., neurosurgery, cardiac surgery, etc.).

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be presented.

9.4.9 EXPLORATORY ANALYSES

Exploratory analyses will include postoperative pain, intensive care unit length of stay, and hospital length of stay.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. Written consent materials are submitted with this protocol.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored on the Research Electronic Data Capture (REDCap) system managed by Washington University School of Medicine. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at Washington University School of Medicine. After the study is completed, the de-identified, archived data will be transmitted to and stored at the National Data Archive, for use by other researchers including those outside of the study.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
Bradley Fritz, MD, MSCI
Washington University School of Medicine
660 S Euclid Avenue, St. Louis, MO 63110
314-273-3453
bafritz@wustl.edu

In addition, an executive steering committee will serve as advisors to the principal investigator.

10.1.6 SAFETY OVERSIGHT

Safety oversight will be performed by an independent safety monitor (ISM). The ISM will be a physician with relevant expertise in the care of postoperative critically ill patients. The ISM will be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The ISM will review adverse events as they reported, according to the timelines outlined in section 8.3.5.

In addition to as-needed reviewing of reportable events, the ISM will review safety data every 6 months. This review will include the following safety outcomes described in section 8.2: psychotomimetic side effects, clinical and adverse events checklist, level of sedation, vital signs during study medication infusion, and nausea/vomiting.

10.1.7 CLINICAL MONITORING

Not applicable

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.]

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by Washington University School of Medicine. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 3 years. These documents should be retained for a longer period, however, if required by local regulations.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents and reported to the funding agency. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 2 years after the completion of the primary endpoint by contacting the principal investigator.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable

10.3 ABBREVIATIONS

AE	Adverse Event
AUDIT	Alcohol Use Disorders Identification Test
BJH	Barnes-Jewish Hospital
BMI	Body Mass Index
BPRS	Brief Psychiatric Rating Scale
CADSS	Clinical Administered Dissociative State Scale
CFR	Code of Federal Regulations
CGI	Clinical Global Impression
CMP	Clinical Monitoring Plan
CONSORT	Consolidated Standards of Reporting Trials
CPAP	Center for Preoperative Assessment and Planning
CRF	Case Report Form
CTQ	Childhood Trauma Questionnaire
DAST	Drug Abuse Screening Test
eCRF	Electronic Case Report Forms
EEG	Electroencephalogram
FDA	Food and Drug Administration
GABA	Gamma-Aminobutyric Acid
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
ICD	International Classification of Disease
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
K-PASS	Ketamine for Postoperative Avoidance of Depressive Symptoms
MADRS	Montgomery-Asberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NIH	National Institutes of Health
NMDA	N-Methyl-D-Aspartate
OHRP	Office for Human Research Protections
PACU	Post Anesthesia Care Unit
PHQ-9	Patient Health Questionnaire-9
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
QIDS	Quick Inventory of Depressive Symptomatology
RASS	Richmond Agitation and Sedation Scale
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SOA	Schedule of Activities
SOP	Standard Operating Procedure
SWA	Slow Wave Activity

UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

1. Horne D, Kehler S, Kaoukis G, et al. Depression before and after cardiac surgery: do all patients respond the same? *J Thorac Cardiovasc Surg.* 2013;145(5):1400-1406.

2. Theunissen M, Peters ML, Schepers J, Schoot DC, Gramke HF, Marcus MA. Prevalence and predictors of depression and well-being after hysterectomy: An observational study. *Eur J Obstet Gynecol Reprod Biol.* 2017;217:94-100.

3. Booth H, Khan O, Prevost AT, Reddy M, Charlton J, Gulliford MC. Impact of bariatric surgery on clinical depression. Interrupted time series study with matched controls. *J Affect Disord.* 2015;174:644-649.

4. Hellstadius Y, Lagergren J, Zylstra J, et al. Prevalence and predictors of anxiety and depression among esophageal cancer patients prior to surgery. *Dis Esophagus.* 2016;29(8):1128-1134.

5. Weekes DG, Campbell RE, Shi WJ, et al. Prevalence of Clinical Depression Among Patients After Shoulder Stabilization: A Prospective Study. *J Bone Joint Surg Am.* 2019;101(18):1628-1635.

6. Barbieri V, Cardinale F, Gozzo F, et al. Risk factors for postoperative depression: A retrospective analysis of 248 subjects operated on for drug-resistant epilepsy. *Epilepsia.* 2015;56(10):e149-155.

7. Ai AL, Smyth SS. Depression After Open Heart Surgery: Influences of Optimism, Sex, and Event-Related Medical Factors. *J Nerv Ment Dis.* 2021;209(3):212-217.

8. Caspi-Avissar N, Grosman-Rimon L, Gohari J, et al. Clinical, Surgical, and Sociopsychological Factors and Depression After Cardiothoracic Surgery. *Ann Thorac Surg.* 2021;111(3):1064-1070.

9. Patron E, Messerotti Benvenuti S, Palomba D. Preoperative and perioperative predictors of reactive and persistent depression after cardiac surgery: a three-month follow-up study. *Psychosomatics.* 2014;55(3):261-271.

10. Goebel S, Steinert A, Vierheilig C, Faller H. Correlation between depressive symptoms and perioperative pain: a prospective cohort study of patients undergoing orthopedic surgeries. *Clin J Pain.* 2013;29(5):392-399.

11. Tully PJ, Baker RA, Turnbull D, Winefield H. The role of depression and anxiety symptoms in hospital readmissions after cardiac surgery. *J Behav Med.* 2008;31(4):281-290.

12. Takagi H, Ando T, Umemoto T. Perioperative depression or anxiety and postoperative mortality in cardiac surgery: a systematic review and meta-analysis. *Heart Vessels.* 2017;32(12):1458-1468.

13. Summary of the clinical practice guideline for the treatment of depression across three age cohorts. *Am Psychol.* 2021 [published online 2021/11/30]. doi:10.1037/amp0000904.

14. Taylor MJ, Freemantle N, Geddes JR, Bhagwagar Z. Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis. *Arch Gen Psychiatry.* 2006;63(11):1217-1223.

15. Nierenberg AA, Farabaugh AH, Alpert JE, et al. Timing of onset of antidepressant response with fluoxetine treatment. *Am J Psychiatry.* 2000;157(9):1423-1428.

16. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry.* 2006;163(1):28-40.

17. Zarate CA, Jr., Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry.* 2006;63(8):856-864.

18. Marcantoni WS, Akoumba BS, Wassef M, et al. A systematic review and meta-analysis of the efficacy of intravenous ketamine infusion for treatment resistant depression: January 2009 - January 2019. *J Affect Disord.* 2020;277:831-841.

19. Murrough JW, Iosifescu DV, Chang LC, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *Am J Psychiatry.* 2013;170(10):1134-1142.

20. Phillips JL, Norris S, Talbot J, et al. Single, Repeated, and Maintenance Ketamine Infusions for Treatment-Resistant Depression: A Randomized Controlled Trial. *Am J Psychiatry.* 2019;176(5):401-409.

21. Chowdhury GM, Behar KL, Cho W, Thomas MA, Rothman DL, Sanacora G. ^{1}H-[^{13}C]-nuclear magnetic resonance spectroscopy measures of ketamine's effect on amino acid neurotransmitter metabolism. *Biol Psychiatry.* 2012;71(11):1022-1025.

22. Li M, Demenescu LR, Colic L, et al. Temporal Dynamics of Antidepressant Ketamine Effects on Glutamine Cycling Follow Regional Fingerprints of AMPA and NMDA Receptor Densities. *Neuropsychopharmacology.* 2017;42(6):1201-1209.

23. Abdallah CG, De Feyter HM, Averill LA, et al. The effects of ketamine on prefrontal glutamate neurotransmission in healthy and depressed subjects. *Neuropsychopharmacology.* 2018;43(10):2154-2160.

24. Zanos P, Moaddel R, Morris PJ, et al. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature.* 2016;533(7604):481-486.

25. Woelfer M, Li M, Colic L, et al. Ketamine-induced changes in plasma brain-derived neurotrophic factor (BDNF) levels are associated with the resting-state functional connectivity of the prefrontal cortex. *World J Biol Psychiatry.* 2020;21(9):696-710.

26. Li N, Lee B, Liu RJ, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science.* 2010;329(5994):959-964.

27. Tononi G, Cirelli C. Sleep function and synaptic homeostasis. *Sleep Med Rev.* 2006;10(1):49-62.

28. Duncan WC, Jr., Selter J, Brutsche N, Sarasso S, Zarate CA, Jr. Baseline delta sleep ratio predicts acute ketamine mood response in major depressive disorder. *J Affect Disord.* 2013;145(1):115-119.

29. Duncan WC, Sarasso S, Ferrarelli F, et al. Concomitant BDNF and sleep slow wave changes indicate ketamine-induced plasticity in major depressive disorder. *Int J Neuropsychopharmacol.* 2013;16(2):301-311.

30. Singh JB, Fedgchin M, Daly EJ, et al. A Double-Blind, Randomized, Placebo-Controlled, Dose-Frequency Study of Intravenous Ketamine in Patients With Treatment-Resistant Depression. *Am J Psychiatry.* 2016;173(8):816-826.

31. Albott CS, Lim KO, Forbes MK, et al. Efficacy, Safety, and Durability of Repeated Ketamine Infusions for Comorbid Posttraumatic Stress Disorder and Treatment-Resistant Depression. *J Clin Psychiatry.* 2018;79(3).

32. Daly EJ, Singh JB, Fedgchin M, et al. Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial. *JAMA Psychiatry.* 2018;75(2):139-148.

33. Popova V, Daly EJ, Trivedi M, et al. Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study. *Am J Psychiatry.* 2019;176(6):428-438.

34. Wajs E, Aluisio L, Holder R, et al. Esketamine Nasal Spray Plus Oral Antidepressant in Patients With Treatment-Resistant Depression: Assessment of Long-Term Safety in a Phase 3, Open-Label Study (SUSTAIN-2). *J Clin Psychiatry.* 2020;81(3).

35. Daly EJ, Trivedi MH, Janik A, et al. Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial. *JAMA Psychiatry.* 2019;76(9):893-903.

36. Lenze EJ, Farber NB, Kharasch E, et al. Ninety-six hour ketamine infusion with co-administered clonidine for treatment-resistant depression: A pilot randomised controlled trial. *World J Biol Psychiatry.* 2016;17(3):230-238.

37. Siegel JS, Palanca BJA, Ances BM, et al. Prolonged ketamine infusion modulates limbic connectivity and induces sustained remission of treatment-resistant depression. *Psychopharmacology (Berl).* 2021;238(4):1157-1169.

38. Brinck EC, Tiippana E, Heesen M, et al. Perioperative intravenous ketamine for acute postoperative pain in adults. *Cochrane Database Syst Rev.* 2018;12(12):Cd012033.

39. Wang J, Xu Z, Feng Z, Ma R, Zhang X. Impact of Ketamine on Pain Management in Cesarean Section: A Systematic Review and Meta-Analysis. *Pain Physician.* 2020;23(2):135-148.

40. Xu Y, Li Y, Huang X, Chen D, She B, Ma D. Single bolus low-dose of ketamine does not prevent postpartum depression: a randomized, double-blind, placebo-controlled, prospective clinical trial. *Arch Gynecol Obstet.* 2017;295(5):1167-1174.

41. Ma JH, Wang SY, Yu HY, et al. Prophylactic use of ketamine reduces postpartum depression in Chinese women undergoing cesarean section(☆). *Psychiatry Res.* 2019;279:252-258.

42. Yao J, Song T, Zhang Y, Guo N, Zhao P. Intraoperative ketamine for reduction in postpartum depressive symptoms after cesarean delivery: A double-blind, randomized clinical trial. *Brain Behav.* 2020;10(9):e01715.

43. Kudoh A, Takahira Y, Katagai H, Takazawa T. Small-dose ketamine improves the postoperative state of depressed patients. *Anesth Analg.* 2002;95(1):114-118, table of contents.

44. Wang J, Wang Y, Xu X, Peng S, Xu F, Liu P. Use of Various Doses of S-Ketamine in Treatment of Depression and Pain in Cervical Carcinoma Patients with Mild/Moderate Depression After Laparoscopic Total Hysterectomy. *Med Sci Monit.* 2020;26:e922028.

45. Mashour GA, Ben Abdallah A, Pryor KO, et al. Intraoperative ketamine for prevention of depressive symptoms after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial. *Br J Anaesth.* 2018;121(5):1075-1083.

46. Ketalar (Ketamine Hydrochloride) injection [package insert]. [published online]. Chestnut Ridge, NY: Par Pharmaceutical; 2017.

47. Krystal JH, Karper LP, Seibyl JP, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry.* 1994;51(3):199-214.

48. Wagner BK, O'Hara DA. Pharmacokinetics and pharmacodynamics of sedatives and analgesics in the treatment of agitated critically ill patients. *Clin Pharmacokinet.* 1997;33(6):426-453.

49. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry.* 1979;134:382-389.

50. Williams JB, Kobak KA. Development and reliability of a structured interview guide for the Montgomery Asberg Depression Rating Scale (SIGMA). *Br J Psychiatry.* 2008;192(1):52-58.

51. Maier W, Heuser I, Philipp M, Frommberger U, Demuth W. Improving depression severity assessment--II. Content, concurrent and external validity of three observer depression scales. *J Psychiatr Res.* 1988;22(1):13-19.

52. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry (Edgmont).* 2007;4(7):28-37.

53. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry.* 2003;54(5):573-583.

54. Flemenbaum A, Zimmermann RL. Inter- and intra-rater reliability of the Brief Psychiatric Rating Scale. *Psychol Rep.* 1973;32(3):783-792.

55. Rodrigues NB, McIntyre RS, Lipsitz O, et al. A simplified 6-Item clinician administered dissociative symptom scale (CADSS-6) for monitoring dissociative effects of sub-anesthetic ketamine infusions. *J Affect Disord.* 2021;282:160-164.

56. Newcomer JW, Farber NB, Jevtovic-Todorovic V, et al. Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. *Neuropsychopharmacology.* 1999;20(2):106-118.

57. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med.* 2006;166(10):1092-1097.

58. Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. *Addiction.* 1993;88(6):791-804.

59. Skinner HA. The drug abuse screening test. *Addict Behav.* 1982;7(4):363-371.

60. Bernstein DP, Stein JA, Newcomb MD, et al. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse Negl.* 2003;27(2):169-190.

61. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract.* 2004;10(2):307-312.

62. Julious SA. Sample size of 12 per group rule of thumb for a pilot study. *Pharmaceut Stat.* 2005;4(4):287-291.