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PHASE I, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED SINGLE-CENTER STUDY ON THE EFFECT OF POSTOPERATIVE ADMINISTRATION OF SINGLE DOSE KETAMINE ON PAIN AND RECOVERY AFTER ROBOTIC REMOVAL OF ENDOMETRIOSIS IN PATIENTS EXPERIENCING CHRONIC PELVIC PAIN

The Using Postoperative Ketamine and Exploring the Effect on Endometriosis Pain (UPKEEEP) Study

Principal Investigator:	Jian Qun (Kathy) Huang, MD Department of Obstetrics and Gynecology 419 Park Avenue South, Suite 1305 Kathy.Huang@nyulangone.org 212-545-5400
Additional Investigators:	Lisa Doan, MD Department of Anesthesiology, Perioperative Care, and Pain Medicine 240 East 38th Street, 14th Floor New York, NY 10016 Lisa.Doan@nyulangone.org 212-201-1004 Steve Calvino, MD Department of Anesthesiology, Perioperative Care, and Pain Medicine 240 East 38th Street, 14th Floor New York, NY 10016 Steve.Calvino@nyulangone.org 212-201-1004 Nikita Nayyar, DO Department of Anesthesiology, Perioperative Care, and Pain Medicine 550 1st Ave, Suite 605, New York, NY 10016 New York, NY 10016 Nikita.Nayyar@nyulangone.org 212-263-5072
NYULMC Study Number:	s21-01032
Funding Sponsor:	Department of Obstetrics and Gynecology 530 First Avenue, Suite 10Q New York, NY 10016 212-263-7021
Study Product:	Ketamine [(+/-)-2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone]
Study Product Provider:	NYU Langone Pharmacy
ClinicalTrials.gov Number	*Include the National Clinical Trial (NCT) Number assigned once the trial is registered on the ClinicalTrials.gov.*

Initial version: 12/16/2021
Amended: 3/23/2022
Amended: [date]

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

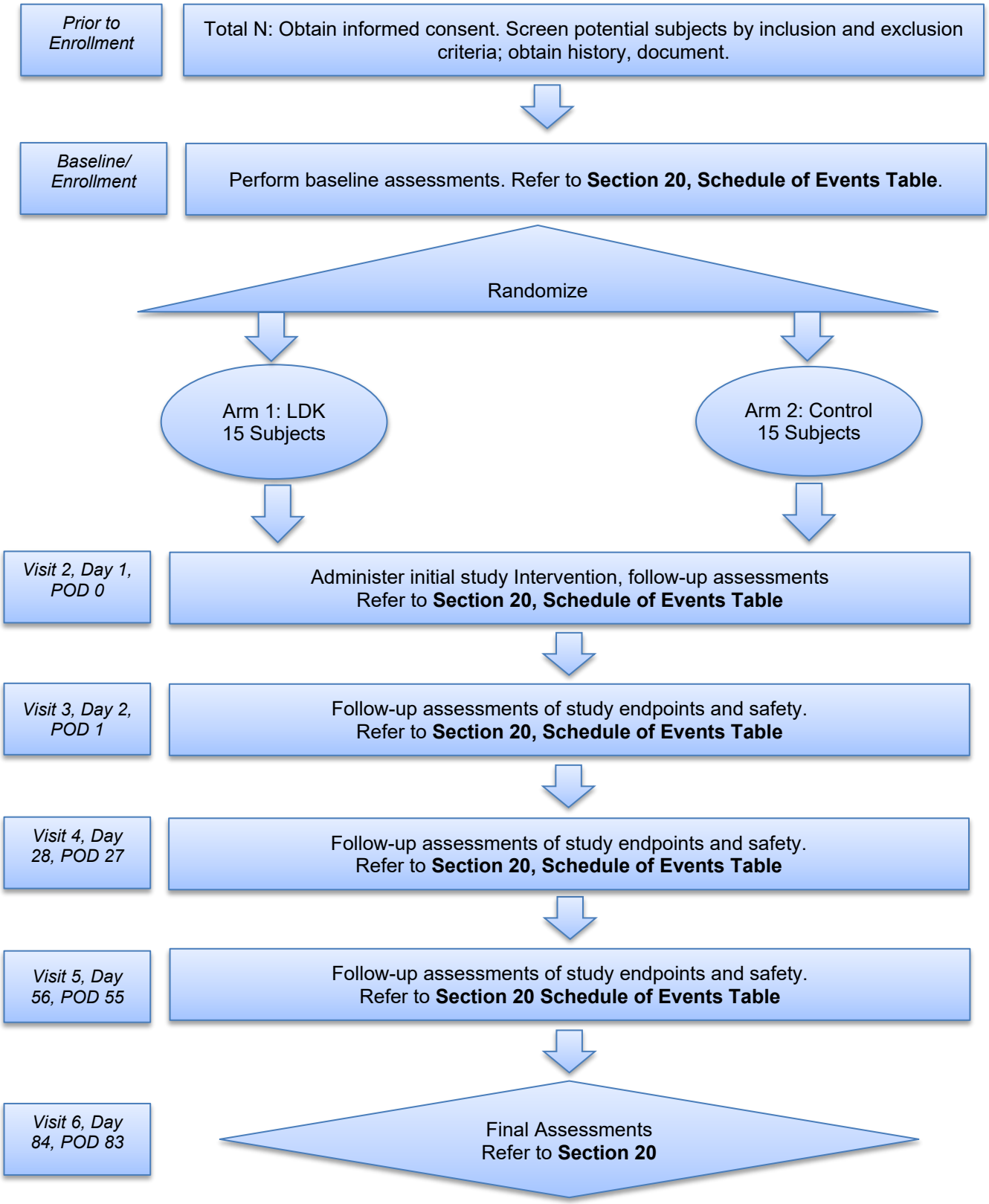
AE	Adverse Event/Adverse Experience
BMI	Body Mass Index
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
ED	Emergency Department
EHP-30	Endometriosis Health Profile - 30)
FFR	Federal Financial Report
FWA	Federal wide Assurance
GAD-7	Generalized Anxiety Disorder - 7
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	Health Related Quality of Life
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IV	Intravenous
IRB	Institutional Review Board
ISM	Independent Safety Monitor
LDK	Low-dose ketamine
MADRS	Montgomery-Asberg Depression Scale
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
OR	Operating Room
PI	Principal Investigator
PACU	Post Anesthesia Care Unit
POD	Post-operative Day
QA	Quality Assurance
QC	Quality Control
RCT	Randomized Controlled Trial

SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States
VAS	Visual Analogue Scale

Protocol Summary

Title	Phase I Randomized, Double-blind, Placebo-controlled, Single-center Study of the Effect of Postoperative Administration of Single dose Ketamine on Pain and Recovery after Robotic Removal of Endometriosis in Patients with chronic pelvic pain
Short Title	The Using Postoperative Ketamine and Exploring the Effect on Endometriosis Pain (UPKEEEP) Study
Brief Summary	This is a randomized, double blinded, placebo-controlled trial to study the effectiveness of a subanesthetic dose (0.6 mg/kg) of ketamine versus placebo (saline) on postoperative pain and pain on adult female chronic pelvic pain patients undergoing robotic removal of endometriosis.
Phase	Phase I
Objectives	To explore the effect of a sub anesthetic dose of ketamine (0.6 mg/kg) vs. saline control on postoperative pain and recovery in chronic pelvic pain patients who have undergone robotic removal of endometriosis.
Methodology	Randomized, double blinded, placebo-controlled trial
Endpoint(s)	Visual Analogue Score (VAS) Endometriosis Health Profile-30 Opiate use General Anxiety Disorder-7 (GAD-7) Montgomery-Asberg Depression Rating Scale (MADRS) Douleur Neuropathique 4 Questions (DN-4) Side Effects Adverse Events
Study Duration	Approximately 10 months
Participant Duration	Approximately 4 months
Duration of IP administration	At least 30 minutes at one time point
Population	Adult women, aged 18-65, with chronic pelvic pain defined as self-reported moderate to severe pelvic pain for > 6 months and scheduled for robotic removal of endometriosis at NYU Langone Health.
Study Sites	NYU Langone Health – Tisch Hospital
Number of participants	30 total participants expected to enroll (15 in treatment group, 15 in control group)
Description of Study Agent/Procedure	Ketamine[(+/-)-2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone] is a white, crystalline powder or clear liquid. Ketamine at a dose of 0.6 mg/kg will be administered intravenously (IV) while the participant is recovering in the PACU. The study drug will be administered over at least 30 minutes at one time point and will be administered after subject has been deemed to be stable (hemodynamically stable, awake) by the study team on POD 0.
Reference Therapy	Saline. Saline is a prescription medicine used for fluid and electrolyte replenishment for intravenous administration. This is placebo drug in this study.
Key Procedures	IV administration of ketamine or saline Self-reported questionnaires Medical records review (opioid use and dosage assessments)
Statistical Analysis	Descriptive statistics will be used to summarize continuous variables. The normality of the distributions for continuous variables will be tested using Q-Q plots and Shapiro–Wilk tests. Differences between arms will be compared with two-sample t-test if outcome is normally distributed or with Wilcoxon's rank-sum test otherwise.

Schematic of Study Design



1 Key Roles

Principle Investigator:
Jian Qun (Kathy) Huang, MD
Assistant Professor, Department of Obstetrics and Gynecology
NYU Grossman School of Medicine
419 Park Avenue South, Suite 1305
212-545-5400
Kathy.Huang@nyulangone.org

Co-Investigator:
Lisa Doan, MD
Associate Professor, Department of Anesthesiology, Perioperative Care, and Pain Medicine
NYU Grossman School of Medicine
240 East 38th Street, 14th Floor
New York, NY 10016
212-201-1004
Lisa.Doan@nyulangone.org

Co-Investigator:
Steve Calvino, MD
Clinical Associate Professor, Department of Anesthesiology, Perioperative Care, and Pain Medicine
240 East 38th Street, 14th Floor
New York, NY 10016
Steve.Calvino@nyulangone.org
212-201-1004

Co-Investigator:
Nikita Nayyar, DO
550 1st Ave, Suite 605, New York, NY 10016
New York, NY 10016
Nikita.Nayyar@nyulangone.org
212-263-5072

Clinical Research Coordinator:
Justin Zaslavsky, BA
Department of Obstetrics and Gynecology
NYU Grossman School of Medicine
419 Park Avenue South, Suite 1305
212-545-5400
Kathy.Huang@nyulangone.org

2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Ketamine is an effective analgesic that can be administered in the perioperative period. Its use as a continuous infusion intra-operatively or postoperatively has been shown to lower pain scores and reduce opioid consumption after surgery.[1–7] Furthermore, ketamine has emerged as a powerful antidepressant and anxiolytic with enduring effects that can last a week.[8–11] Ketamine doses below 1mg/kg can be considered low-dose ketamine (LDK), sub-anesthetic, or sub-dissociative.[1,2,7,12–15] In emergency department settings, LDK is a safe and effective non-opioid form of long-lasting post-discharge pain relief. [2–4,16,17]

Single dose ketamine, as opposed to an infusion, can produce similar effects. It suppresses hyperactive neurons in the anterior cingulate cortex (ACC), a brain region well known to regulate the affective component of pain. A single ketamine bolus (0.3-0.6 mg/kg) can effectively activate cortical top-down processing for mood and pain regulation. [2–4,12,15,17–20]

A recent randomized controlled trial (RCT) of single-dose ketamine in the post-anesthesia care unit (PACU) found that single dose ketamine reduced the affective component of pain for 7 days after bariatric surgery.[21] This study involved 0.4 mg/kg dose of ketamine among patients with low baseline levels of depression and anxiety. In our current study, we have increased the effective dose to 0.6 mg/kg which is in the therapeutic dose range for mood disorders and pain in the emergency department.[2,12,17,20] This dosage aligns our study with an ongoing trial exploring the effect of postoperative ketamine among mastectomy patients at NYU Langone Health. We hypothesize that the slightly increased single bolus dose of ketamine may be more helpful in certain surgical populations experiencing chronic pain and/or those with high baseline depression and anxiety scores, such as patients with endometriosis and chronic pelvic pain.

Endometriosis is a troubling gynecologic disorder that causes endometrial tissue to grow outside of the uterus. The condition affects 6 to 10% of women of reproductive age, 50 to 60% of women and teenage girls with pelvic pain, and up to 50% of women with infertility. For the roughly 176 million affected worldwide, pelvic pain is the most common symptom. The pain is usually chronic (lasting ≥6 months) and is associated with dysmenorrhea (in 50 to 90% of cases), dyspareunia, deep pelvic pain, and lower abdominal pain with or without back and loin pain.[22]

Furthermore, the condition can impact fertility, sexual health, and quality of life.[23] Endometriosis is considered a disabling condition that may significantly compromise social relationships, sexuality, and mental health. The condition is associated with a wide range of psychiatric symptoms, the most common being depression and anxiety.[24–27]

Ketamine may be a promising therapy for both the chronic pain and psychosocial components of this disease. We hypothesize that a single dose (0.6 mg/kg) administration of ketamine after surgery may relieve postoperative pain, improve mood and short-and-long term recovery, and decrease opioid requirements in patients undergoing robotic removal of endometriosis.

Thirty subjects undergoing robotic endometriosis excision surgery (also known as robotic removal of endometriosis) will be randomized to receive a single bolus ketamine (0.6 mg/kg or placebo control (equal volume saline) administered after surgery in the PACU. All subjects will receive standard of care routine postoperative multimodal analgesia throughout hospital stay and after discharge. The primary endpoint will be the assessment of postoperative pain via the Visual Analogue Scale (VAS), a simple technique for measuring subjective pain experience. The VAS has been established as valid and reliable in a range of clinical applications, including the measurement of postoperative pain.[28–30] The VAS is currently performed by staff as part of the postoperative treatment plan. Secondary endpoints include the Endometriosis Health Profile-30 – A Health Related Quality of Life (EHP - HRQoL), General Anxiety Disorder-7 (GAD-7), and Montgomery–Asberg Depression Rating Scale (MADRS). These three questionnaires are valid, reliable, and easy to implement.[10,23,31–36] Opiate use will be assessed through medical records and subject reports.

Side effects and adverse events will also be assessed as reported by patients or observed by study team members.

Descriptive statistics will be used to summarize continuous variables. The normality of the distributions for continuous variables will be tested using Q-Q plots and Shapiro–Wilk tests. Differences between arms will be compared with two-sample t-test if outcome is normally distributed or with Wilcoxon's rank-sum test otherwise.

2.2 Name and Description of the Investigational Agent

Ketamine [(+/-)-2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone] is a white, crystalline powder or clear liquid. It is a schedule III substance and is classified as a dissociative anesthetic. Ketamine is available as a racemic mixture with the S- (+)- isomer being more potent than the R- (-)- isomer. It is commercially supplied as the hydrochloride salt in 0.5 mg/mL and 5 mg/mL ketamine base equivalents. Clinically, it is commonly used as an anesthetic induction agent for diagnostic and surgical procedures prior to the administration of general anesthetics. It is also used as a low dose infusion for analgesia.

Ketamine is an FDA-approved general anesthetic and analgesic agent that has been safely used clinically over the last 50 years. For general anesthesia, the induction dose ranges from 1mg/kg to 4.5 mg/kg. At sub anesthetic doses (< 1mg/kg), ketamine is a potent analgesic with a clinically effective half-life of 45 min. It is also a powerful antidepressant and anxiolytic as a single dose (0.3-0.6 mg/kg), which can produce up to 14 days of mood stabilization.

Saline is a prescription medicine used for fluid and electrolyte replenishment for intravenous administration. 0.9% normal saline will be used as the placebo in the control group.

2.2.1 Dose Rationale

Ketamine is often administered as a continuous infusion. However, single doses have also been used and are simpler to implement. In previous studies for depression and pain, a dose range of 0.3-0.6 mg/kg 1 was used. In our prior study of ketamine for bariatric surgery, investigators used a single dose of 0.4 mg/kg for ideal body weight. To further evaluate a single dose of ketamine for postoperative pain, this study uses 0.6 mg/kg, which falls in the range of the therapeutic dose for mood disorders and pain.[1,2,7,12,14,15,20] The study drug is a 0.6 mg/kg dose of ketamine that will be administered intravenously as a single bolus dose to participants. A matching volume of 0.9% normal saline will be used as the placebo in the control group.

2.3 Rationale

The treatment of chronic pelvic pain is a crucial element of proper gynecologic care, accounting for 10% of outpatient gynecologic visits.[22] Endometriosis is observed in 71 to 87 percent of women with chronic pelvic pain.[37] For some, robotic removal of the endometriosis is recommended to relieve symptoms. Ketamine's powerful analgesic effects may be helpful for pain management in the perioperative period as well as throughout long-term recovery.[24–27]

Patients with endometriosis have a higher probability of prolonged opioid use compared to their counterparts without endometriosis.[38] Over-prescription and irrational opioid use lead to excessive drug dependence and drug abuse, resulting in an increased mortality rate and huge economic loss.[39] In addition to the ongoing opioid crisis, preoperative opioid use has been shown to be independently associated with increased costs and worse outcomes after major abdominal surgery.[40] Ketamine serves as a safe and effective alternative to opiates for pain management.[4,20]

Women with endometriosis also suffer increased rates of psychological morbidities including depression and anxiety. Ketamine has been used as an effective antidepressant and anxiolytic to manage psychological and mood-related symptoms.[2–4,12,15,17–20]

We hypothesize that postoperative use of ketamine can lead to an improvement in pain indices, a decrease in opioid requirement, and improvements in mood as measured by psychometric indices in subjects undergoing robotic removal of endometriosis.

30 subjects (15 in each arm) will be accrued. Women scheduled for robotic removal of endometriosis and classified as having chronic pain (defined as experiencing moderate or severe pelvic pain for greater than six months) will be screened for eligibility to participate in this study. Prospective subjects will be recruited, screened, and consented prior to surgery. Subjects will be adult women (aged 18-65), as endometriosis usually affects women of reproductive age, and the study will be conducted at an adult care practice (opposed to a pediatric or adolescent practice).[22,37] There is no limitation for subjects as to racial and ethnic origin. The study population was chosen because of the opportunity to manage pain via ketamine and their elevated risk for opioid use and mental health disorders.

Protocol and study procedures will be reviewed with study team members and study physicians. Protocol adherence will be recorded and verified through patient's electronic medical records.

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

The risks for ketamine are well studied. In general, ketamine is a well-tolerated medication.[1,6,14,20] There may also be risks that are currently unforeseeable.

Psychological Effects: Psychological side effects have included decreased awareness of general environment, sedation, dream-like state, vivid dreams, feelings of invulnerability, increased distractibility, disorientation, and general uncommunicativeness. Additionally, hallucinations, impaired thought processes, delirium, out-of-body experiences, and changes in perception about body, surroundings, time, and sounds can occur. Emergence reactions have occurred in approximately 12 percent of subjects.[41]

Physiological: Anesthesia, cataplexy, immobility, tachycardia, increased blood pressure, nystagmus, hypersalivation, increased urinary output, profound insensitivity to pain, amnesia, slurred speech, and lack of coordination can occur.

Cardiovascular: Cardiovascular side effects have included elevated blood pressure and heart rate following administration of ketamine alone. However, hypotension and bradycardia have also been observed. Other arrhythmias such as ventricular tachycardia are rare.

Respiratory: Respiratory side effects have included stimulated respiration, although severe depression of respiration or apnea may occur following rapid intravenous administration of ketamine. Laryngospasms and other forms of airway obstruction have occurred during ketamine anesthesia. Additionally, hypersalivation or the increased production of salivary and tracheobronchial secretions can occur, which may be clinically significant during extubation or post-op airway protection.

Ocular: Ocular side effects have included diplopia, nystagmus, and a slight elevation in intraocular pressure.

Oral: Hypersalivation can occur during ketamine administration.

Gastrointestinal: Gastrointestinal side effects have included anorexia, nausea, and vomiting. It is possible that severe nausea and vomiting may occur during the post-op period due to the dual effects of the recent general anesthetic and ketamine administration.

Musculoskeletal: Musculoskeletal side effects have included enhanced skeletal muscle tone manifested by tonic and clonic movements sometimes resembling seizures.

Local: Local side effects have included pain and exanthema at the injection site.

Dermatologic: Dermatologic side effects have included transient erythema and/or morbilliform rash.

Psychiatric: Psychiatric side effects have included anxiety, euphoria, dysphoria, illusions, hallucinations, flashbacks, blunted affect, catatonia, and psychotic episodes.

Neurologic: Impaired attention/memory/judgment, disorientation, delirium, diplopia, and blurred vision.

Urinary: Increased urinary output; rarely cystitis.

Duration of Effects: Onset of analgesic effect of ketamine is within 1-5 minutes if injected. The effects of ketamine generally last 30-45 minutes if injected as a single bolus. However, some residual symptoms such as nausea and vomiting may persist longer than general effects.

Drug Interactions: Benzodiazepines may decrease ketamine-associated emotional distress but does not decrease cognitive or behavioral effects of ketamine. Acute administration of diazepam increases the half-life of ketamine. Lamotrigine significantly decreases ketamine-induced perceptual abnormalities but increases the mood elevating effects. Haloperidol may decrease impairment by ketamine in executive control functions, but does not affect psychosis, perceptual changes, negative schizophrenic-like symptoms, or euphoria. Alfentanil is additive to ketamine in decreasing pain and increasing cognitive impairment. Physostigmine and 4-aminopyridine can antagonize some pharmacodynamic effects of ketamine.

Contraindications include increased intracranial pressure (ICP), glaucoma, or acute globe injury. Caution is advised in patients with cardiovascular illness, porphyria, or thyroid disorder.

Side effects typically end 30 minutes after the termination of infusion. These risks will be mitigated using the strategies described in the protection against risks and dose adjustments sections. There are no expected side effects associated with the administration of saline.

There are no known side effects associated with completing the questionnaires. There may be some mild level of fatigue associated with answering the questions.

Confidentiality risks: The risk is privacy violation via the unexpected release of protected health information contained in health records or research data or the release of randomization information. As a result, this study involves the possibility of psychological and social risks related to breach of confidentiality.

2.4.2 Protection against Risks

Given that ketamine will be given in the recovery room, all participants will be monitored by the study care team and PACU physicians for any of the effects mentioned above. To minimize the risk of physiological effects and cardiovascular side effects, the single bolus ketamine dose will be given over at least a 30-minute period. For the risks of psychomimetic side effects, such side effects may be treated with reassurance.

The investigators have many layers of protection to minimize the risk of inadvertent release of protected health information. The methods for de-identification of data will mitigate this risk. We will take all necessary precautions to maintain complete confidentiality of data and prevent unauthorized access to the data. Data will only be collected from subjects who consent and whose physicians deem safe to proceed with data collection. Participants will be allowed to exit the study at any time. Participants who withdraw consent will be counseled that their withdrawal only affects uses and sharing of information after their written request to withdraw authorization has been received, and that their authorization may not be withdrawn for uses or disclosures that have previously been made or need to be made to complete analyses or report data from the research. For the confidentiality of randomization, only the physician administering the study drug will know which group the subject(s) is/are in for both the experimental and control group.

All data and records generated during this study will be kept confidential in accordance with institutional policies and HIPAA on subject privacy. The study investigators will not use such data and records for any purpose other than conducting the study. Privacy protection procedures are in place and good clinical practice guidelines will be followed throughout the study to minimize the risks associated with breach of confidentiality. This risk will be minimized by strict compliance with HIPAA procedures for securing PHI. Information that could be used to identify the subject will only be shared with researchers who have approval of the IRB.

2.4.2 Known Potential Benefits

Perioperative ketamine improves pain and reduces opioid use in the acute postoperative period. Additionally, other benefits may include a reduction in depression and anxiety symptoms and improvements in long-term pain management and function. There is a potential benefit gained by study subjects for better postoperative analgesia and mood elevation as well as faster recovery from surgery.[1–5,7–10,20,42] There is also a potential for longer term benefit on the affective component of pain from the mood elevating effects of ketamine.[5,16] Furthermore, there is benefit to society in gaining a better understanding of postoperative analgesic and mood elevating strategies, physical function, quality of life, and opioid use requirements. It is possible some study subjects will not benefit but future patients may benefit from this study.

3 Objectives and Purpose

This study will evaluate the effects of a postoperative single 0.6 mg/kg dose of ketamine on pain and recovery in patients having undergone robotic removal of endometriosis. Pain, mood, anxiety, quality of life, physical function, and opioid use will also be measured.

3.1 Primary Objective

The primary objective is to examine the effect of a sub anesthetic dose of ketamine (0.6 mg/kg) vs. saline control on postoperative pain in chronic pelvic pain patients who have undergone robotic removal of endometriosis measured using the VAS.

3.2 Secondary Objectives (if applicable)

The secondary objective is to examine the effects of a sub anesthetic dose of ketamine (0.6 mg/kg) vs. saline control on pain, short- and long-term recovery (anxiety, quality of life, and physical function), and opioid use in patients experiencing chronic pelvic pain who have undergone the robotic removal of endometriosis. Incidence of side effects will also be evaluated.

4 Study Design and Endpoints

4.1 Description of Study Design

This is a phase 1 randomized, double-blind, placebo-controlled, two-arm parallel, single-center study.

30 subjects (15 in each arm) will be accrued. Randomization lists will be sent only to the study physician administering study drug. Participant and assessor of outcome measures will be blinded. The surgeon, anesthesiologist, and the research team members conducting the follow up visits will not know which group the subjects are assigned to. Only the physician administrating the study will be aware of whether ketamine or placebo is administered, and this provider will not be a part of any outcome measure data collection. The investigators conducting and reviewing the outcome measures will be blinded.

Adult women, aged 18-65, with chronic pelvic pain (defined as moderate to severe self-report > 6 months) will be screened for eligibility to participate in this study. Prospective subjects will be recruited, screened, and consented prior to surgery. On the day of the surgery, Eligible subjects will be randomized to one of the two groups in a 1:1 ratio to receive either intravenously (IV) ketamine (0.6 mg/kg) or matching equal dose of placebo. Subjects will receive either the study drug or placebo while recovering in the post anesthesia care unit (PACU) on the day of the surgery after subject has been deemed to be stable

(hemodynamically stable, awake). The study drug or placebo will be administered by study physicians who are anesthesiologists. The study physician will administer the study intervention via an intravenous pump to deliver 0.6 mg/kg ketamine or equal volume saline over at least 30 minutes.

Participation in the study will not alter the subject's surgical or anesthetic care, post-anesthetic care, or standard of care on the floor. All subjects will also receive standard post-anesthetic monitoring and care, as well as routine care after transferring out of the PACU. There is no restriction on the use of other analgesics throughout this study. Subjects are followed, and endpoints (see below) are collected from subject reports as well as from medical charts (opioid use).

Patient demographics recorded include age, date of birth, race, MRN, gender, ethnicity, participant enrollment location, zip code, and disease site.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

The primary endpoint will be the assessment of pelvic pain using the Visual Analogue Scale (VAS) at enrollment date, POD 1, POD 27, POD 55, and POD 83. The VAS is a clinically relevant, valid, and reliable measure of pain.[28–30] Post-operative participant self-reported scores will be used to determine the efficacy of the test drug in pain management.

4.2.2 Secondary Study Endpoints

The secondary endpoints will examine short- and long-term recovery, opioid use, side effects and adverse events.

1. Endometriosis Health Profile-30 (EHP-30): A Health-Related Quality of Life (HRQoL) patient self-report tool used to measure the wide range of effects that endometriosis can have on patients' lives, including work, relationship with child/children, sexual relationship, feelings about medical profession, feelings about treatment, and feelings about infertility. This report will be completed on the enrollment date, POD 1, POD 27, POD 55, POD 83. The EHP-30 will be used to measure the quality-of-life component of short- and long-term recovery.

2. General Anxiety Disorder-7 (GAD-7): A Self-administered 7 item instrument that uses some of the DSM-V criteria for General Anxiety Disorder to identify probable cases of GAD along with measuring anxiety symptom severity. The GAD-7 assessments will be completed on the enrollment date, POD 1, POD 27, POD 55 and POD 83. The GAD-7 will be used to measure the anxiolytic effects of the test drug.

3. Montgomery-Asberg Depression Rating Scale (MADRS): A 10 item questionnaire often used by psychiatrists to measure the severity of depressive episodes in patients with mood disorders. MADRS assessments will be completed on the enrollment date, POD 1, POD 27, POD 55 and POD 83. The MADRS will be used to measure the antidepressant effects of the test drug.

4. Douleur Neuropathique 4 Questions (DN-4): This 10 item questionarre identifies neuropathic pain, which ketamine has been shown to address. This will allow for subgroup analyses that can shed light on best practice for these patients. The DN-4 will be completed at baseline by the study physician.

5. Opioid use: The opioid use and dosage assessment will be assessed through medical records and subject reports. Assessment of opiate use will be used to determine the opiate-sparing effects of the study drug. Opioid use and dosage assessments will be completed on the enrollment date, POD 0, POD 1, POD 27, POD 55, and POD 83.

6. Assessment of Side Effects: A questionnaire will assess any potential side effects of the intervention at POD 0, POD 1, and POD 27.

7. Assessment of Adverse Events: Assessment of adverse events as reported by participant or observed by investigator and study team The assessment of adverse events will be completed at the enrollment date, POD 1, POD 27, POD 55 and POD 83. Events will be recorded via study database.

5 Study Enrollment and Withdrawal

Prospective subjects will be screened, recruited, and consented prior to their surgery date. Participants will be screened during the surgical consult by the study surgeon, who may give potential participants a one-pager with key information on the study. Should the patient meet the inclusion criteria (see below) and are interested in participating, they will be referred to (their information will be shared with) a clinical research coordinator on the study team who will call prospective subjects or arrange a video conference session (WebEx only). Eligible patients will be invited to participate in the study and the research coordinator will answer any outstanding questions and begin the informed consent process.

The subject will remotely receive a link to the informed consent, sign, and return informed consent document through a REDCap link. The link to the REDCap e-consent will be submitted to the IRB via modification following initial approval. The study team will not use the REDCap e-consent until it has been IRB approved. The prospective subject will be emailed a copy of the informed consent form. Once informed consent is given, the study team member will provide the participant with information regarding the next steps for participation. Consent may be obtained up to two months before surgery at the earliest, but will occur no less than 2 days before a subject's surgery at the latest..

5.1 Inclusion Criteria

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

1. Adults, aged 18 to 65 years old
2. Experiencing chronic pain, defined as experiencing moderate to severe pelvic pain for greater than 6 months
3. Scheduled to undergo robotic endometriosis removal surgery
4. Willing to comply with all study procedures and be available for the duration of the study.
5. Subject is medically stable.

5.2 Exclusion Criteria

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

1. Cognitive impairment (by history) or clinical signs of altered mental status such as confusion, amnesia, disorientation, fluctuating levels of alertness, etc. that may interference with adherence to study procedures and/or participant safety.
2. Past ketamine or phencyclidine misuse or abuse
3. Schizophrenia or history of psychosis
4. Known sensitivity or allergy to ketamine
5. Liver or renal insufficiency.
6. History of uncontrolled hypertension, chest pain, cardiac arrythmia, stroke, head trauma, intracranial mass or hemorrhage or pressure, glaucoma, acute globe injury, uncontrolled thyroid disease, porphyria, or any other contraindication to ketamine. Use of lamotrigine, alfentanil, physostigmine, and 4-aminopyridine are contraindicated
7. Pregnancy or nursing women
8. Currently participating in another pain interventional trial
9. Unwillingness to give informed consent
10. Non-English-speaking patients as the EHP-30 instrument has only been licensed to NYULH in English.

5.3 Vulnerable Subjects

Vulnerable subject populations will not be included in this study. The study will not enroll Children, pregnant women, fetuses, neonates, prisoners, or persons with decisional incapacity.

5.4 Strategies for Recruitment and Retention

This study will utilize EPIC to identify prospective subjects.

The privacy of prospective subjects will be protected during the identification process. All members of the research team will have access to EPIC. The research team will consist of study surgeons, investigators, treating physicians and research coordinators. Study staff members are experienced at consenting patients or prospective subjects for anesthesiology studies, and they include physicians as well as qualified designated team members. Eligible patients or prospective subjects will be assessed for capacity to give informed consent by a study team member. The study team does not anticipate any subjects will have questionable or impaired capacity. As such, judgment that prospective subjects have the capacity to consent to the research can ordinarily be made informally during routine interactions with the individual during the consent process as described in section 11.6 of the NYU SOM IRB Policy and Procedures document. Medical status/stability will be addressed by members of the research team. Eligible patients or prospective subjects will be invited to participate in the study. Data will be discarded at least 3 years after closing out or 5 years after final reporting, whichever is longer, by deleting from the network.

Any recruitment information sent by email will utilize Send Safe email.

To first screen for eligible subjects, participating study surgeons, investigators, treating physician will review their appointment, operating, and other schedules on EPIC to identify eligible patients or prospective subjects for study recruitment. Eligible patients are those described in Section 5.1: diagnoses with endometriosis, experiencing chronic pain, and scheduled or being scheduled for a robotic removal of endometriosis surgery. Research team members may also screen for eligible prospective subjects on all participating physicians' schedules on EPIC and will contact these prospective subjects on their behalf with permission of study surgeons, investigators, and/or treating physician. The subjects' data will be screened to see if they match the study's eligibility criteria. The research team members will search EPIC as many times as needed until all 30 eligible subjects are recruited. Once eligible subjects are identified, recruitment can either be in-person or over the phone.

1. Recruited in-person
   A research team member will speak to the eligible subject during appointments at NYU Langone Gynecology locations including outpatient facilities and hospitals. The study surgeon may also talk to subjects about the study during their appointment and can refer subjects who are eligible. Surgeons may give potential participants the IRB-approved research flyer with key information document to introduce the study. Once a subject has been referred, a study team member will call the subject through the "recruitment and enrollment over the phone" strategies listed below. Should the potential subjects agree, the study team member will complete the informed consent process.

2. Recruitment and enrollment over the phone
   a. The IRB-approved telephone script will be used to communicate the reason participants are being contacted. They will be asked if they are interested in participating in this specific study. Research team members will call prospective subjects or arrange a video conference session (WebEx only). The study team member will then ask pre-screening questions, and if deemed eligible, the study team member will explain the consent to the prospective subject and ask if the prospective subject has any questions before the prospective subject electronically signs. The study team will immediately destroy any information collected from subjects who are either determined to be ineligible or who are eligible but decide not to enroll in the study. If the prospective participant agrees, they will be sent a copy of the informed consent via REDCap. The prospective subject will remotely receive a link to the informed consent form, sign, and return informed consent document through REDCap.

Once informed consent is given, the study team member will provide the prospective subjects with information regarding the next steps for participation. Consent may occur up to two months before surgery. Subjects will also be consented no less than 2 days before their surgery.

If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact research-contact-optout@nyumc.org or 1-855-777-7858.

The inclusion and exclusion criteria in this study should not have a negative effect on the enrollment of the desired populations. Treatment will take place at the NYU Langone Health Tisch/Kimmel Hospital under the supervision of the PI. Prospective subjects will receive detailed information regarding this study; its investigational nature, required study procedures, alternative treatments, risks, and potential benefits of the study. They will also receive the informed consent document to read. All questions are answered by the PI and qualified research personnel.

Recruitment and consenting will take place in a private area such as exam room (if in person) or remotely (phone call and video conference call) to protect the patient or prospective subject's privacy.

We anticipate recruitment to take approximately 5 months.

5.5 Duration of Study Participation

Participant participation will last up to 84 days starting at enrollment. There are 6 visits in total, each visit lasting less than 1 hour.

5.6 Total Number of Participants and Sites

Target accrual for this study is 30 subjects. Recruitment will end when approximately 50 participants are enrolled. It is expected that approximately 50 participants will be enrolled in order to maintain 30 participants for the duration of the study. The sites include NYU Langone Health Tisch/Kimmel Hospital.

5.7 Participant Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request for any reason, and without repercussion. Participants who withdraw consent will be counseled that their withdrawal only affects uses and sharing of information after their written request to withdraw authorization has been received, and that their authorization may not be withdrawn for uses or disclosures that have previously made or need to be made to complete analyses or report data from the research. For the confidentiality of randomization, only the physician administering the study drug will know which group the subject(s) is/are in for both experimental and control group. All data and records generated during this study will be kept confidential in accordance with institutional policies and HIPAA on subject privacy. The study investigators will not use such data and records for any other purpose other than conducting the study. Privacy protection procedures are in place and good clinical practice guidelines will be followed throughout the study to minimize the risks associated with breach of confidentiality. This risk will be minimized by strict compliance with HIPAA procedures for securing PHI. Information that could be used to identify the subject will only be shared with researchers who have approval of the IRB.

The investigator and sponsor have the right to discontinue a subject from study treatment or withdraw a subject from the study at any time. If a subject is discontinued from the study at the discretion of a PI or other delegated individual, the reason for discontinuation procedures will be noted in the subject's research record.

An investigator may terminate participation in the study if, but are not limited to:

- Subject withdrawal of consent at any time

- Disease progression
- Intolerable toxicity
- Any medical condition that the investigator or sponsor determines may jeopardize the subject's safety if the subject continues treatment with the study drug
- The investigator or sponsor determines it is in the best interest of the subject
- Failure of the subject to adhere to protocol procedure requirements
- Study termination by sponsor
- 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
- The participant meets an exclusion criterion (either newly developed or not previously recognized) before surgery that precludes further study participation.

Criteria for discontinuing study intervention includes but not limited to:

- Allergic reaction thought to be related to study drug
- Uncontrolled hypertension, hypotension, or arrhythmia thought to be related to study drug
- Severe psychomimetic side effects
- Medical events/logistical reasons not related to study therapy

Study physician will be responsible for determining whether study interventions will be discontinued, based on his or her clinical judgement. In the case of cardiovascular side effects, if such side effects persist despite treatment based on PACU clinician's decisions, study drug may be discontinued. The reason for the dose discontinuation should be documented.

Psychomimetic side effects will be monitored by study and PACU physicians. Such side effects may be treated with reassurance. If participants continue to complain of anxiety or dysphoria or are agitated, pharmacologic agents (such as benzodiazepines) may be administered based on clinical judgement of PACU clinicians. If psychomimetic side effects are felt to be severe, with severe hallucinations, delusions, or agitation, study drug will be discontinued.

Additionally, in the event of any discontinuation of study intervention, with consent, participants will continue with the completion of remaining study visits.

5.7.2 Handling of Participant Withdrawals or Termination

Subjects, who choose to withdraw consent, can do so by notifying the treating physician, the Principal Investigator or research staff in writing or verbally. Any data remaining after formal withdrawal, will be destroyed/discarded per Institutional guidelines. Subject will be informed whether the data will be retained and analyzed up to the point of withdrawal. The study team will document the reason for discontinuation in the subjects' research record. Every effort will be made to undertake protocol-specified safety follow-up procedures to capture AEs, serious adverse events (SAEs), and unanticipated problems (UPs). If subjects withdraw or discontinue early replacement participants will be allowed.

5.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

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

- Determination of unexpected, significant, or unacceptable risk to participants.
- Demonstration of efficacy that would warrant stopping.
- Insufficient compliance to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination of futility.

Study may resume once concerns about safety, protocol compliance, and/or data quality are addressed and satisfy the sponsor, IRB.

6 Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

Ketamine is an FDA-approved general anesthetic and analgesic agent that has been safely used clinically over the last 50 years. For general anesthesia, the intravenous induction doses range from 1 mg/kg to 4.5mg/kg. At subanesthetic doses (<1mg/km), ketamine is a potent analgesic with a clinically effective half-life of 45 min.[6,43,44] Off label it is also used as a powerful antidepressant and anxiolytic as a single dose (0.3-0.6 mg/kg) which can produce up to 14 days of mood stabilization.[8–10,45]

This study is IND exempt as 21 CFR 312.2(b)(1) and 21 CFR 312.2(b)(5) as the study meets all the following criteria:

1. The drug product is lawfully marketed in the US.
2. The investigation is not intended to be reported to FDA as a well-controlled study in support of new indication and there is no intent to use it to support any significant change in the labeling of the drug.
3. In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
4. The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increase the risk (or decreases the acceptability of the risk) associated with the use of the drug product.
    a. The risks for ketamine are well studied. In general, ketamine is a well-tolerated medication.[1,6,14,20] In previous studies for depression and pain, a dose range of 0.3-0.6 mg/kg was used. In a prior NYU study of ketamine for bariatric surgery, we used 0.4 mg/kg for ideal body weight.31 To further evaluate a single dose of ketamine for postoperative pain, we will use 0.6 mg/kg, which is in the range of the therapeutic dose for mood disorders and pain.[1,2,7,12,14,15,20,21]
5. The investigation is conducted in compliance with the requirements for review by an IRB and with the requirements for informed consent.
6. The investigation is conducted in compliance with 21 CFR 312.7 (no intention to promote or commercialize the drug product).
7. The clinical investigation involves a placebo **and** the investigation does not otherwise require submission of an IND (refer to the sections above).

6.1 Study Agent(s) and Control Description

Ketamine [(+/-)-2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone] is a white, crystalline powder or clear liquid. It is a schedule III substance and is classified as a dissociative anesthetic. Ketamine is available as a racemic mixture with the S- (+)- isomer being more potent than the R- (-)- isomer. It is commercially supplied as the hydrochloride salt in 0.5 mg/mL and 5 mg/mL ketamine base equivalents. Clinically, it is commonly used as an anesthetic induction agent for diagnostic and surgical procedures prior to the administration of general anesthetics. It is also used as a low dose infusion for analgesia.

Ketamine is an FDA-approved general anesthetic and analgesic agent that has been safely used clinically over the last 50 years. For general anesthesia, the induction dose ranges from 1mg/kg to 4.5 mg/kg. At sub anesthetic doses (< 1mg/kg), ketamine is a potent analgesic with a clinically effective half-life of 45 min. It is also a powerful antidepressant and anxiolytic, as a single dose (0.3-0.6 mg/kg) which can produce up to 14 days of mood stabilization.

Saline is a prescription medicine used for fluid and electrolyte replenishment for intravenous administration. 0.9% normal saline will be used as the placebo in the control group.

6.1.1 Acquisition

Ketamine or saline will be ordered and obtained from NYULH inpatient pharmacy.

6.1.2 Formulation, Appearance, Packaging, and Labeling

Ketamine is a nonbarbiturate general anesthetic chemically designated dl 2-(0-chlorophenyl)-2(methylamino) cyclohexanone hydrochloride. It is formulated as a slightly acidic (pH 3.5-5.5) sterile solution for intravenous or intramuscular injection. Ketamine is available from NYULH inpatient pharmacy in concentrations of 50 mg/ml.

Saline is a prescription medicine used for fluid and electrolyte replenishment for intravenous administration. It will serve as the placebo drug in this study.

6.1.3 Product Storage and Stability

The study drug should be stored between 20° to 25°C (68° to 77°F).

The control solution, 0.9% normal saline will be stored at temperatures between 20° 25°C (68° to 77°F).

6.1.4 Preparation

The study drug will be obtained from NYULH inpatient pharmacy (212-263-5048). The study physician is not blinded. Ketamine will be diluted to 10 mg/ml in normal saline by study physician. 0.9% normal saline will be used as the control.

6.1.5 Dosing and Administration

Single bolus ketamine: For the single bolus dose arm, ketamine at a dose of 0.6 mg/kg will be administered while the participant is recovering in the PACU on the day of surgery. The study drug will be administered over at least 30 minutes at one time point and will be administered after subject has been deemed to be stable (hemodynamically stable, awake) by the study team on POD 0.

Control/Placebo: Participants randomized into this group will receive matching volume of saline infusion in the PACU over at least 30 minutes at one time point (no ketamine).

6.1.6 Route of Administration

The planned route of administration is intravenous for the ketamine study drug and placebo drug.

6.1.7 Duration of Therapy

Approximately 30 Minutes.

6.1.8 Tracking of Dose

Drug protocol adherence will be recorded and verified through patient's electronic medical record and REDCap.

6.2 Study Agent Accountability Procedures

Study drug will be ordered by study physician when participant arrives to PACU. Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed, and dated by the study team. Unused study drug will be wasted with witness.

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

7.1.1 Study Specific Procedures

- *Assessment of eligibility should include a review of permitted and prohibited medications.*
- *Assessment of study agent adherence*
- *Assessment of current and former Opioid Use*
- *Assessment of Side Effects/Adverse Events*
- *Administration of Visual Analogue Scale for pelvic pain assessment*
- *Administration of questionnaire packet including: EHP-30, GAD-7, and MADRS*

7.1.2 Standard of Care Study Procedures

- *Medical history*
- *Medication history*

7.2 Study Schedule

7.2.1 Screening

Screening/Introductory Visit (Day -28 to -1)

- Introduce study and discuss participation
- Obtain medical history and medications history
- Review and verify inclusion/exclusion criteria
- Refer eligible participants to research coordinator
- Schedule baseline visit for participants who have been screened for eligibility and interested in participating and/or learning more about the study

7.2.2 Enrollment/Baseline

Enrollment/Baseline Visit (Visit 1, Day 0)

- Review and verify inclusion/exclusion criteria
- Obtain informed consent of potential participant verified by signature on written informed consent or electronic consent
- Obtain demographics information
- Complete baseline/enrollment survey
- Identify and document endometriosis staging
- Identify and document final procedure(s) list
- Review and verify medical history, medication history, and demographic information
- VAS assessment of pelvic pain
- Subjects will complete the questionnaire packet for assessments which will include, EHP-30, GAD-7, DN-4, and MADRS questionnaires. Opioid use and adverse events will also be assessed via subject reporting and medical record review. This will be done either in person, over the phone, or electronically via REDCap link sent to subject

7.2.3 Intermediate Visits

Study Visit 2 (Visit 2, Day 1, POD 0)

- Perform randomization
- Administer the study intervention, ketamine single dose or placebo. Administration of normal saline placebo is standard of care
- Assessment of opioid use and dosage assessment via subject reporting and medical record review
- Assessment of adverse events and side effects as reported by participant or observed by investigator and study team.

- Document interoperative ketamine administration

Study Visit 3 (Visit 3, Day 2, POD 1)

- Participant will be asked to which treatment arm they believe they have been assigned
- VAS assessment for pelvic pain
- Subjects will complete a questionnaire packet including the EHP-30, GAD-7.and MADRS
- Assessment of opioid use and dosage assessment via subject reporting and medical record review
- Assessment of adverse events and side effects as reported by participant or observed by investigator and study team
- If participant is still in the hospital, study staff may administer questionnaires in person or electronically via REDCap
- If the participant has already been released from the hospital, a research team member will either send the subject an electronic REDCap link to the questionnaires or call the subject to answer the questionnaires on the phone

Study Visit 4 (Visit 4, Day 28, POD 27)

- VAS assessment for pelvic pain
- Subjects will complete a questionnaire packet including the EHP-30, GAD-7 and MADRS
- Assessment of opioid use and dosage assessment
- Assessment of adverse events and side effects as reported by participant or observed by investigator and study team
- If participant is still in the hospital, study staff may administer questionnaires in person or electronically via REDCap
- If the participant has already been released from the hospital, a research team member will either send the subject an electronic REDCap link to the questionnaires or call the subject to answer the questionnaires on the phone.

Study Visit 5 (Visit 5, Day 56, POD 55)

- VAS assessment for pelvic pain
- Subjects will complete a questionnaire packet containing EHP-30, GAD-7 and MADRS
- Assessment of opioid use and dosage assessment
- Assessment of adverse events as reported by participant or observed by investigator and study team
- If participant is still in the hospital, study staff may administer questionnaires in person or electronically via REDCap
- If the participant has already been released from the hospital, a research team member will either send the subject an electronic REDCap link to the questionnaires or call the subject to answer the questionnaires on the phone.

7.2.4 Final Study Visit

Study Visit 6 (Visit 6, Day 84, POD 83)

- VAS assessment for pelvic pain
- Subjects will complete a questionnaire packet including the EHP-30, GAD-7 and MADRS
- Assessment of opioid use and dosage assessment
- Assessment of adverse events as reported by participant or observed by investigator and study team

7.2.5 Withdrawal/Early Termination Visit

Participants are free to withdraw from participation in the study at any time upon request. However, participants should be counseled that they may request stopping the interventional drug but continue to be in the study. They also will be told that follow-up for adverse events is recommended for safety.

Lost to follow-up is defined by the inability to reach a participant after a minimum of two phone calls. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

7.2.6 Unscheduled Visit

Unscheduled visits will be documented in the subjects' record.

7.3 Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications, and non-prescription medications.

7.4 Justification for Sensitive Procedures

We will use 0.9% saline as the control. The solution Saline is a prescription medicine used for fluid and electrolyte replenishment for intravenous administration. It will serve as the placebo drug in this study. Using a placebo will help the study team better assess the role of the study drug, 0.6 mg/kg ketamine, on study outcomes.

7.5 Rescue Medications, Treatments, and Procedures

Cardiovascular side effects may be treated based on PACU clinician's decisions. If such side effects persist despite treatment, study drug may be halted.

Psychomimetic side effects will be monitored by study and PACU physicians. Such side effects may be treated with reassurance. If participants continue to complain of anxiety or dysphoria or are agitated, pharmacologic agents (such as benzodiazepines) may be administered based on clinical judgement of PACU clinicians. Benzodiazepine administration will be at discretion of PACU clinician; midazolam in titrated doses of 0.5-1 mg could be considered. If psychomimetic side effects are felt to be severe, with severe hallucinations, delusions, or agitation, study drug will be discontinued.

8 Assessment of Safety

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness, or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.1.3 Definition of Unanticipated Problems (UP) Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all the following criteria:

- Unexpected in nature, severity, or frequency (i.e., not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e., 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)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

For 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.

8.2.2 Study Agent

The clinician's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- ***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 drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (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 drug, 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.

- ***Possibly 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 drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) 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 drug 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.*

8.2.3 Expectedness

The principal investigator will be responsible for determining whether an 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 agent.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or 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 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. UPs will be recorded in the data collection system throughout the study.

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 PI 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.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.4 Notifying the IRB

8.4.1 Adverse Event Reporting

The PI 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 contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs and symptoms should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be definitely and probably related to the study treatment or study participation should be recorded and reported immediately.

8.4.2 Serious Adverse Event Reporting

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats, and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported within 5 or 10 days of PI notification are those that are:

- related to study participation,
- unexpected, and
- Harmful or have the potential to cause harm

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, related and unrelated, will be recorded on the SAE Form and submitted within 24 hours of site awareness.
- Other SAEs will be submitted within 72 hours of site awareness.

This information should be reported to the PI and to the DSMC. All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly.

Adverse events that do not fit the above immediately reportable criteria must still be reported to the IRB at each annual review, either in a summary or tabular format.

8.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the Data Coordinating Center (DCC)/study sponsor. 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 that are SAEs will be reported to the IRB 5 or 10 days of the investigator or the study team becoming aware of the event. Unexpected death of unknown causality and any event requiring immediate intervention to prevent subject harm requires 5 calendar days.
- Any other UP will be reported to the IRB within 5 or 10 days of the investigator or the study team becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 5 or 10 days of the IRB's receipt of the report of the problem from the investigator and the study team.

8.4.4 Reportable Events

The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation). Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file. The Principal Investigator is responsible for reporting all unexpected problems involving risk to participants or others.

8.5 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at the site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events. The data safety monitoring plan is as follows:

The individuals responsible for data safety and monitoring will be Kathy Huang, MD and Nikita Nayyar, DO. A conflict of interest will be avoided by study team's full disclosure of conflicts as per NYULH standards.

Quality control will include regular data verification and protocol compliance checks by Germaine Cuff, PhD.

Drs. Huang and Nayyar will complete quarterly reports detailing the study progress and subject status, any adverse events, and any protocol deviations. Specific data to be reviewed in the quarterly reports include: pelvic pain scores, general anxiety scores, depression scores, opioid use and dosage, and any adverse events reported to or observed by the study team including but not limited to side effects of the study drug. Protocol adherence (specifically, the participants' completing the assigned surveys) will be monitored by Justin Zaslavsky, Research Coordinator. All other aspects of protocol compliance will be reviewed by Dr. Cuff.

Throughout the study, the study team will monitor the participants for adverse events. Events determined by the Principal Investigator (PI) to be unanticipated problems involving risks to subjects or others (UPIRTSOs) will be reported by the PI to the IRB within 10 days per policy. Adverse events that are determined by the PI to not be UPIRTSOs will be reported per IRB policy at the time of continuing review. Reference section 5.8 for specific stop criteria to be used by the study team.

All study staff members will be informed by Justin Zaslavsky about any UPIRTSOs. If any protocol changes are needed, the PI will submit a modification request to the IRB (and VA R&D if applicable). Protocol changes will not be implemented prior to IRB approval unless necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the IRB will be promptly informed of the change following implementation (within 10 working days). The Study team will also submit an annual report with the Continuing Review Submission.

Statistical review of the study will be conducted by Yan Zhang at the end of all study visits for all subjects. Interim analyses will be performed by Yan Zhang to assess equity. If inequity occurs, consideration will be given to stopping the study early. In the event of early stopping of the study, the IRB will be promptly notified.

9 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s). The completeness, accuracy and consistency of the data, and adherence to ICH Good Clinical Practice guidelines will be followed.

10 Statistical Considerations

10.1 Statistical Hypotheses

The primary outcome will be the assessment of postoperative pain using the Visual Analogue Scale (VAS) between the ketamine and placebo arms at enrollment date, POD 1, POD 27, POD 55, and POD 83. We hypothesize that subjects who receive ketamine will have lower postoperative pain scores at all time points than those who receive placebo. Secondary outcomes include changes in opioid use between the ketamine and control arms, as well as changes in Endometriosis Health Profile-30, General Anxiety Disorder-7 (GAD-7), and Montgomery-Asberg Depression Rating Scales (MADRS). We hypothesize that subjects who receive ketamine will have decreased opioid use, as well as lower scores on the mood and quality of life scales above than those who receive placebo.

10.2 Analysis Datasets

The study dataset consists of 30 subjects; 15 of whom will be randomized to receive a sub anesthetic single bolus of ketamine (0.6 mg/kg) following robotic removal of endometriosis and 15 of whom will be randomized to receive an equal volume saline bolus as control. All analyses will be treated as intention to treat based on the randomization of study subjects to either the ketamine arm or placebo arm.

10.3 Description of Statistical Methods

10.3.1 General Approach

This is a phase 1, randomized, double blind placebo controlled single center study to determine the effects of a postoperative single 0.6 mg/kg dose of ketamine on pain and recovery in patients having undergone robotic removal of endometriosis. Mood, anxiety, quality of life, physical function, and opioid use will also be measured.

Descriptive statistics will be used to summarize continuous variables with mean and standard deviation, or categorical variables with frequency and percentage. The normality of the distributions for continuous variables will be tested using Q-Q plots and Shapiro–Wilk tests. If the distribution is skewed, continuous variables will be summarized using median and the inter-quartile range. A two-sided p-value<0.05 will be considered statistically significant. All analyses will be conducted using R.

10.3.2 Analysis of the Primary Efficacy Endpoint(s)

The primary endpoint is postoperative pain assessed via the Visual Analogue Scale (VAS) at enrollment date, POD 1, POD 27, POD 55, and POD 83. The difference between the two arms (ketamine vs placebo) will be compared using Wilcoxon's rank sum test. To account for repeated measurements of postoperative pain scores on days 1, 27, 55, and 83, a mixed model repeated measures (MMRM) method

will be used. This model will include the baseline pain scale, treatment, time, treatment by time interaction, and unbalanced baseline variables as relevant. Model based least square means will be obtained and reported at each time point.

10.3.3 Analysis of the Secondary Endpoint(s)

Secondary endpoints include opioid dosage as well as scales for mood and quality of life. The difference in secondary outcomes between ketamine and placebo will be compared using Wilcoxon's rank sum test. Secondary outcomes will likewise be obtained on more than one occasion (POD 1, POD 27, POD 55, and POD 83), so an MMRM approach will also be used to assess differences between the two treatment arms. The MMRM models will include treatment, time, treatment by time interaction, preoperative values, and unbalanced baseline variables.

10.3.4 Safety Analyses

Descriptive statistics will be used to summarize side effects of the intervention at POD 0, POD 1, and POD 27 as well as adverse events as reported by participant or observed by the investigator at POD 1, POD 27, POD 55, and POD 83.

10.3.5 Adherence and Retention Analyses

Adherence will be tracked and reviewed using REDCap as well as Epic for ketamine administration. Participant retention and any reasons for discontinuation will be carefully recorded and summarized.

10.3.6 Baseline Descriptive Statistics

Descriptive statistics will be used to summarize the demographic and baseline characteristics, with mean and standard deviation for continuous variable, or frequency and percentage for categorical variables. If continuous variables are skewed, the median and inter-quartile range will be used as well. To test differences in the demographic and baseline characteristics between the two arms, clinical variables that are continuous will be compared using either two sample t-test if normally distributed or Wilcoxon's rank-sum test otherwise and categorical variables will be compared using Chi-squared or Fisher's exact test. Unbalanced baseline variables will be determined by both statistical and clinical significance.

10.3.7 Planned Interim Analysis

Not applicable to our study.

10.3.7.1 Safety Review

As iterated above, this study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Proposed reasons for stopping study enrollment or the study intervention include determination of unexpected and significant risk to participants, demonstration of efficacy or futility that warrants stopping, and insufficient compliance to protocol. Adverse effects will be monitored carefully in the PACU, and then again on POD 1, POD 27, POD 55, and POD 83.

10.3.8 Additional Sub-Group Analyses

All analyses are provided above; there will not be additional sub-group analyses.

10.3.9 Multiple Comparison/Multiplicity

Not applicable to our study.

10.3.10 Exploratory Analyses

All analyses are specified as above; there are not planned exploratory analyses.

10.4 Sample Size

This is a pilot study with limited resources so that it is not powered to detect a hypothesized effect size for VAS. We expect to randomize 15 participants to each arm. With 15 subjects per arm, we have 80% power to test an effect size of 1.1 with a significance level (alpha) of 0.05 using a two-sided Wilcoxon's rank-sum test assuming data are generated from normal distributions.

10.4.1 Enrollment/Randomization/Masking Procedures

The subjects will be randomized in a 1:1 ratio. The treatment subjects will receive 0.6 mg/kg of the study drug, and the control subjects will receive an equal volume of saline. Participants will be randomized with random size permuted blocks, blinded with respect to treatment assignments. Dr. Kathy Huang (the PI) will generate the randomization list.

10.4.2 Evaluation of Success of Blinding

The subject will be asked if they know what group they were placed in at POD 1. If they are unsure that will be evaluated as successful blinding.

10.4.3 Breaking the Study Blind/Participant Code

In this double-blind study, the blind will not be broken.

11 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

An electronic database capture system will be created to record the data for this trial. Research coordinators will input clinical trial data into the database. This database is password protected and only the PI, assigned study team members, and CTO staff will have access to the database. DataCore, a core resource of the

institution, will provide the primary data collection instrument for the study. All data requested in the system must be reported. All missing data must be explained. The quality assurance specialists will monitor this trial every 3 months for data entry accuracy.

REDCap (Research Electronic Data Capture) is a secure web application capture system that will be created to record the data for this study. This database is password protected; the PI and designated study team personnel will have access to the database. REDCap is the primary data collection instrument for this study. All data requested in the system must be reported. All missing data must be explained. The quality assurance specialists will monitor this trial every 3 months for data entry accuracy.

Source documentation refers to original records of observations, clinical findings, and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into any electronic medical record or REDCap. Relevant source documentation to be reviewed by the DSMC throughout the study includes:

1. Baseline measures to assess pre-protocol status
2. Concurrent medications
3. Treatment records
4. Adverse events

Data Collection
Principal Investigator and IRB approved study personnel trained on this protocol will identify subjects. The following data elements will be captured from the subject's medical record and entered into the research database by the assigned data/research coordinator:

- age/ date of birth
- race
- MRN
- gender
- ethnicity
- participant enrollment location
- zip code

12 Quality Assurance and 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 SOPs, the monitors will verify that the clinical trial is conducted, and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the 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.

This study will be monitored according to the monitoring plan detailed below. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g., pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit. A risk-based, data-driven monitoring approach will be used to verify data for this trial which will also include a centralized review of data for quality, trends, consistency, and general safety review. A quality assurance specialist will make regularly scheduled trips to the investigational site to review the progress of the trial, study data and site processes. At each visit, the monitor will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and study manual and with the principles of Good Clinical Practice;

completion of case report forms; source data verification; study drug accountability and storage; facilities and staff.

During scheduled monitoring visits, the investigator and the investigational site staff must be available to meet with the quality assurance specialist in order to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor. In addition to on-site monitoring visits, the Sponsor and/or representatives will also be routinely reviewing data. Any queries identified through this review will be managed within the systems established for query resolution and tracking. Inquiries related to study conduct, which require further information or action will be discussed within the study team for appropriate and documented escalation plans. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database.

At any time during the course of the study, representatives of regulatory agencies may review the conduct or results of the study at the investigational site. The investigator must promptly inform the IRB of any audit requests by health authorities and will provide sponsor with the results of any such audits and with copies of any regulatory documents related to such audits.

In accordance with HIPAA and associated privacy regulations, a patient's authorization to use personal identifiable health information may be required from each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the 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. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

13.3.2 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. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families.

Consent forms will be 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.

All participants will receive a verbal explanation in terms suited to their 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 relatives 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. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. 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.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g., use of a translator, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

13.4 Posting of Clinical Trial Consent Form

The informed consent form will be posted on the Federal website after the clinical trial is closed to recruitment and no later than 60 days after the last study visit by any subject, as required by the protocol. Per institutional guidelines, SOP#: HSR-601, instructs the principal investigator on registration and results reporting on clinicaltrials.gov.

13.5 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. 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.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB 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 local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. 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. This will be their REDCap record ID. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. This will be done in REDCap, and only approved study team members will have access to the database (the REDCap project). At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. 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. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a HIPPA-compliant data capture system provided by MCIT. 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.

14.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, 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 E6:

- 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 PI/study staff to use continuous vigilance to identify and report deviations within 5 or 10 days of identification of the protocol deviation, or within 5 or 10 working days of the scheduled protocol-required activity.

Protocol deviations must be reported to the IRB per guidelines. The PI/study staff is responsible for knowing and adhering to their IRB requirements.

15 Study Finances

15.1 Funding Source

This study is funded by the NYU Langone Health Department of Obstetrics and Gynecology.

15.2 Costs to the Participant

There is no additional cost for participation in this study. The costs associated with participation in this research will be billed to the study. Subject and her health insurance will be responsible for costs associated with the surgical procedure or standard of care, including the placebo (saline).

15.3 Participant Reimbursements or Payments

Subjects will not receive payment for participation this this study.

16 Study Administration

16.1 Study Leadership

The PI and the investigators of the research team will oversee subjects screening, subject recruitment, study visits, and study procedures.

17 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 trial. The study leadership in conjunction with the NYU CIMU has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

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19 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

- Consent Form
- Flyer
- Letter to patients
- Recruitment and consent script
- Demographics
- Pain medication usage
- Treatment arm question
- Visual Analogue Scale
- Endometriosis Health Profile-30 (EHP-30)
- General Anxiety Disorder-7 (GAD-7)
- Montgomery-Asberg Depression Scale (MADRS)
- Douleur Neuropathique 4 Questions (DN4)
- Assessment of opioid use
- Assessment of Adverse Events
- Assessment Side Effects

20 Schedule of Events

STUDY ASSESSMENTS & PROCEDURES	*Screening (Day -60 to -2)*	*Baseline/ Enrollment (Visit 1, Day 0)*	*(Visit 2, Day 1, POD 0)*	*(Visit 3, Day 2, POD 1)*	*(Visit 4, Day 28, POD 27)*	*(Visit 5, Day 56, POD 55)*	*(Visit 6, Day 84, POD 83*
Introduce study and discuss participation	X						
Refer eligible participants to research coordinator	X						
Review and verify of Inclusion/Exclusion Criteria	X	X					
Informed Consent		X					
Demographics[1]		X					
Medical history and medication history	X	X					
Randomization and administer study intervention ketamine single-dose infusion or placebo			X				
Documentation of staging and procedures							
Participants will be asked which treatment arm they believe they have been assigned				X			
Assessment of Pelvic Pain using a Visual Analogue		X		X	X	X	X
Endometriosis Health Profile-30 (EHP-30)		X		X	X	X	X
General Anxiety Disorder-7 (GAD-7)		X		X	X	X	X
Montgomery-Asberg Depression Scale (MADRS)		X		X	X	X	X
Douleur Neuropathique 4 Questions (DN4)		X					
Opioid use and dosage assessment (medical records) and subject reports		X	X	X	X	X	X
Assessment of Adverse Events		X	X	X	X	X	X
Side Effects			X	X	X		

[1]Demographics should be collected, includes: age/ date of birth, race, MRN, gender, ethnicity, and disease.