Ketamine Tolerated Dose to Prevent Postpartum Depression and Pain after Cesarean Delivery (PREPARE 1)

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History of Protocol Versions:

Version	Date	Sections Changed	Rationale for the Change
1.0	April 26, 2023	N/A	N/A
2.0	May 30, 2023	5.2 inclusion criteria 5.4 payment plan 6.4 storage in lockbox 7.4 patient safety	IRB comment response
3.0	June 6, 2023	5.4 payment plan	
4.0	September 12, 2023	Various	Update consistency with MOP DSMB edits
5.0	September 22, 2023	1 5.2	Study population clarification Updated inclusion wording
6.0	December 7, 2023	Protocol Overview Section 4 Section 5.2 Section 5.3	Updated wording for clarity Revised wording to make timing of assessments clearer Revised inclusion criteria to clarify only cesarean delivery, removal of neuraxial morphine restriction as it is not germane to the primary study objectives, specified term delivery definition Revised exclusion criteria to clarify patient undergoing general anesthesia to match wording in other documents; other wording modification to match wording in institutional protocol; removed contraindication to NSAID as it is not germane to primary study objective

		Section 7.1 Section 7.6 Section 8.2 Section 9.2	Updated screening procedures to reflect workflow optimization Corrected a spelling error Deleted "risks of withholding breastfeeding for 60 hours" as we are not asking women to withhold breastfeeding Spelling error
7.0	May 16, 2024	Appendix 3 Appendix 2 Figure 1 Section 3.4.1, 6.3, Table 1 of Section 6.2	Corrected to include protocol-listed assessments at postpartum week 12, which is Day 84, Visit 13 Corrected RASS and vital signs to line up with protocol text LSD >8 cutoff for PI notification and bedside check to enhance safety and facilitate direct event attributions Corrected to line up with protocol text for RASS, side effect assessments and postpartum assessments DLT event definition revised to include complete infusion cessation due to intolerable side effect acceptability ratings by patient. Table now specifies events that qualify as DLT in accordance with revised DLT definition

		Section 6.2	Added grace period range +15 minutes for maintenance infusion dose adjustment times
		Sections 3.4.1, 6.3, 9.1, 12.3, Table 1 of Section 6.2	Reduced systolic blood pressure cutoff from 190mmHg to 160mmHg in accordance with DSMB recommendations and to be more aligned with systolic blood pressure cutoffs in the pregnant and postpartum population
		Section 6.6	Clarified rescue medication protocol for nausea/vomiting

Contents

ABBREVIATIONS AND ACRONYMS

AE	Adverse Event
ADL	Activities of Daily Living
ASA PS	American Society of Anesthesiologist Physical Status
AUC	Area Under Curve
CD	Cesarean Delivery
CFR	Code of Federal Regulations
Cmax	Peak concentration of "drug"
CRF	Case Report Form
Css	Concentration of "drug" at Steady State
DHHS	Department of Health and Human Services
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
EPDS	Edinburgh Postnatal Depression Scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IDS	Investigational Drug Service
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intention-To-Treat
IV	Intravenous
MDD	Major Depressive Disorder
MTD	Maximum Tolerate Dose
NCT	National Clinical Trial
NIH	National Institutes of Health
NMDA	N-Methyl-D-Aspartate Receptor
PCP	Phencyclidine
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetic
PPD	Postpartum Depression
PSS	Perceived Stress Scale
RASS	Richmond Agitation Sedation Scale
REDCap	HIPAA compliant data management software
RID	Relative Infant Dose
SAE	Serious Adverse Event
SSRI	Selective Serotonin Reuptake Inhibitor
UPMC	University of Pittsburgh Medical Center

1 Protocol Overview

Study Description	The purpose of this study is to identify a tolerable dose for postpartum ketamine infusion using a maximum tolerated dose (MTD) 3+3 design. A loading dose over 1 hour will be the MTD variable to be tested, as our data suggest that ketamine side effects occur with the loading dose.
Study Population:	Patients having cesarean delivery (CD) who are either: 1) planning not to breastfeed; or 2) are receiving ketamine as part of clinical care, will be enrolled. Ketamine will be started in postpartum patients, after cord clamping.
Planned Sample Size:	The projected sample size will be a maximum of 12 patients with complete primary outcome data within the MTD 3+3 design.
Participating Institutions (if a multi-center clinical trial)	N/A

1.1 Study Schema

Figure 1. Assessment timeline for MTD study and follow-up assessments

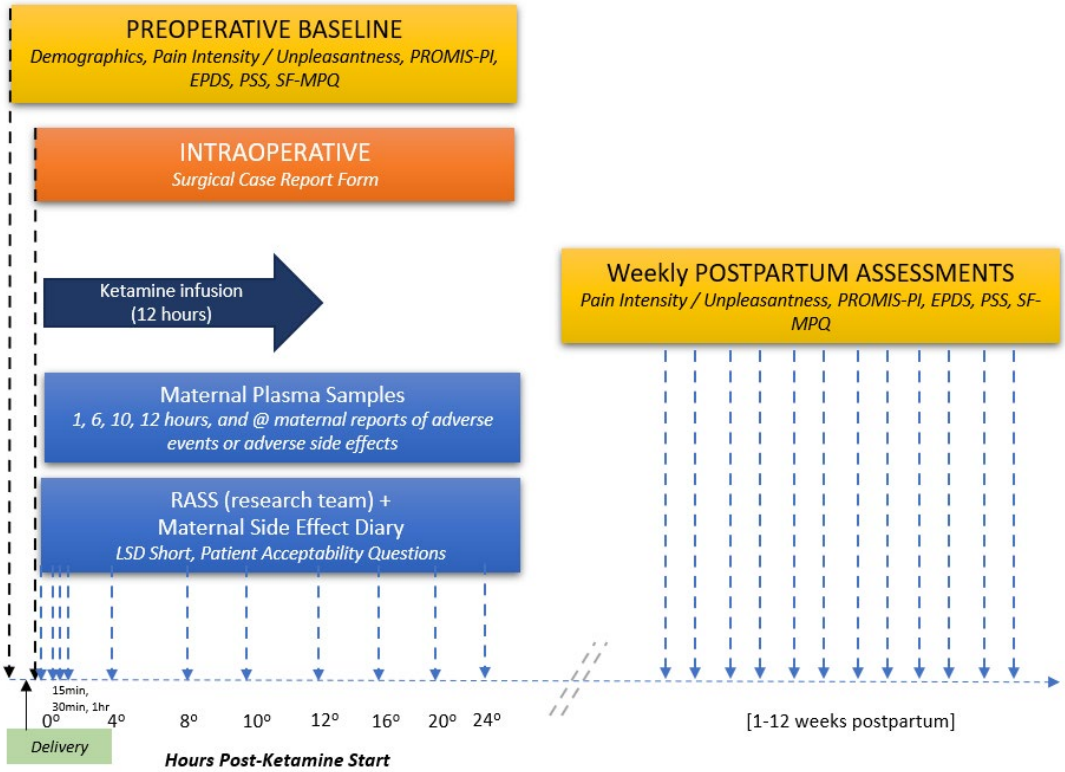
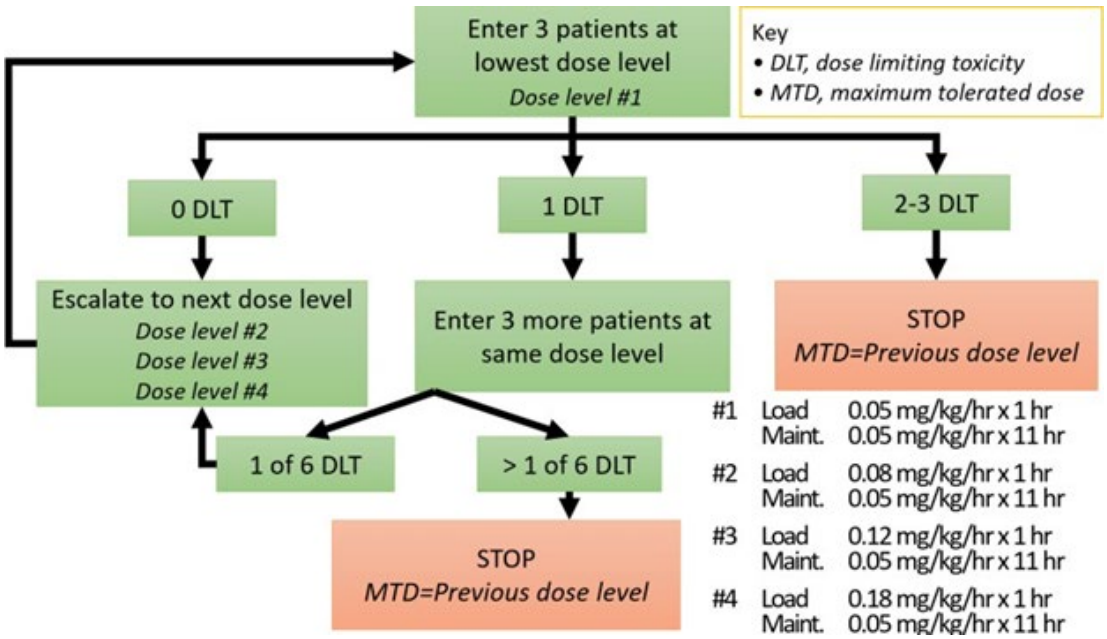


Figure 2. MTD dosing schematic for PREPARE 1.



2 Background and Rationale

2.1 Background

A lack of data on new pain treatments in pregnancy and lactation puts 1.2 million US women having cesarean delivery (CD) every year at risk for poor pain control, depressed mood, and poor recovery[7,8]. Despite high individual variability in pain after CD[6,9], current CD treatments ignore the multidimensionality of pain, including the influence of mood on pain. NMDA receptor antagonists like ketamine significantly reduce postoperative pain and opioid use by up to 40%[10]. In addition to its analgesic effects, a single dose of IV ketamine has been shown to rapidly reduce depressive symptoms by 50% and remission rates 43-77%[86] in non-obstetric populations. Evidence of successful post-surgical pain management and rapid reduction of depressive symptoms render ketamine a great candidate for post-CD pain management and potential reduction of PPD symptomology.

Ketamine at sub-anesthetic doses is effective in post-surgical acute pain management, with long-lasting analgesia. Many trials (non-obstetric) have shown ketamine effectiveness for post-operative analgesia[94-96]. Available postpartum ketamine studies have focused on various doses (ranging 0.1-0.5 mg/kg, single doses, infusions) for efficacy[16-18,66], but have not emphasized side effects. Although high doses of ketamine induce psychomimetic effects, low doses, such as in the current proposal, can reduce pain without side effects[10,78] and potentially reduce pain intensity for 1 year after a single dose (effect size 0.61, 95% CI 0.40 – 0.80)[97].

In addition to its analgesic effects, ketamine use for depression treatment promotes fast, effective depression symptom reductions, a robust effect occurs from 4-72 hours post-infusion (0.5 mg/kg over 40 min) in patients with MDD; this dose is commonly used for depression[87]. The antidepressant effect lasts beyond psychotomimetic symptoms, which peak during the infusion and return to baseline within 1-2 hours[86]. These findings contrast traditional antidepressants whereby only 1/3 of patients become symptom-free after 7 weeks of treatment with SSRI.[85] A widely cited trial of 205 ketamine doses (0.5mg/kg, 40 min) for depression concluded ketamine was, "safe and well- tolerated" but did not probe patient acceptability of side effects[33]. Dose-dependent side effects are common, with a high incidence of vertigo, nausea, sedation, and dissociation in intranasal dosing to plasma levels similar to an IV dose of 0.5 mg/kg over 40min[88]. These dose-dependent side effects preclude widespread use in the peripartum population. Identifying ketamine dose tolerability in a post-CD population has the potential to improve treatment of postoperative pain as well as mood-related outcomes of chronic pain such as comorbid onset of PPD. This work will

Defining postpartum ketamine PK is critical to understanding the potential role of ketamine for PPD prevention, and to understanding the plasma ketamine concentration time profile with its maximum tolerated dose. There are no PK/PD models for ketamine-induced side effects or analgesia, although there are isolated reports of ketamine side effects with plasma concentrations. Available trials that conclude ketamine is "well tolerated" did not query patient perspectives in acceptability[33]. The duration of ketamine exposure may be important as well, given that subcutaneous administration may have greater antidepressant duration than intravenous administration of the same dose, despite lower

peak plasma concentrations in subcutaneous administration[19]. These knowledge gaps are significant because they limit patient-centered acceptability of ketamine and a finer understanding of its potential effective utility for PPD prevention. Because ketamine is metabolized by CYP3A and CYP2B6 (increased activity in pregnancy and immediately after delivery)[34], and because pregnancy induces sensitivity to anesthetics, it is critical in this project to identify a tolerable dose of postpartum ketamine and the perioperative factors impacting its PK.

2.2 Rationale

Defining postpartum ketamine tolerable doses and ketamine PK is critical to understanding the potential role of ketamine for PPD prevention, and to understanding the plasma ketamine concentration time profile with its maximum tolerated dose. There are no PK/PD models for ketamine-induced side effects or analgesia, although there are isolated reports of ketamine side effects with plasma concentrations. Available trials that conclude ketamine is "well tolerated" did not query patient perspectives in side effect acceptability[33]. The duration of ketamine exposure may be important as well, given that subcutaneous administration may have greater antidepressant duration than intravenous administration of the same dose, despite lower peak plasma concentrations in subcutaneous administration[19]. These knowledge gaps are significant because they limit patient-centered acceptability of ketamine and a finer understanding of its potential effective utility for PPD prevention. Because ketamine is metabolized by CYP3A and CYP2B6 (increased activity in pregnancy and immediately after delivery)[34], and because pregnancy induces sensitivity to anesthetics, it is critical in this project to identify a tolerable dose of postpartum ketamine and the perioperative factors impacting its PK.

3 Hypotheses, Objectives and Endpoints

3.1 Hypotheses

3.2 Primary Hypothesis

The purpose of this study is to identify a tolerable dose for postpartum ketamine infusion using a maximum tolerated dose (MTD) 3+3 design. A loading dose over 1 hour will be the MTD variable to be tested, as our data suggest that ketamine side effects occur with the loading dose.

Our working hypothesis, based on our preliminary PK and safety data and that of Loo et al [19], is that a 12-hr IV ketamine infusion of 0.05 mg/kg/hour is the MTD.

3.3 Objectives

3.3.1 Primary Objective:

Quantify maximum tolerable dose of postpartum ketamine infusion post-cesarean delivery.

3.3.2 Secondary Objective

Quantify ***side effect*** acceptability of low-dose ketamine infusion in peripartum people.

3.3.3 Exploratory Objectives

Measure maternal pain and depression in this cohort before and after cesarean delivery until 12weeks postpartum.

3.4 Endpoints

3.4.1 Primary Endpoint

Maximum Tolerated Dose (MTD). The MTD will be defined as the dose at which fewer than 33% of patients experience a DLT defined by intolerability.

Tolerability (dichotomous Yes/No)

Tolerability (YES) will be defined as: lack of adverse events (adverse event defined as: severe unresolved hemodynamic effect: systolic blood pressure <80 or >160, heart rate <40 or >120).[33]

Lack of Tolerability will be defined as presence of any adverse event (i.e., severe unresolved hemodynamic effect: systolic blood pressure <80 or >160, heart rate <40 or >120).[33]

A **DLT** event is defined by complete infusion cessation due to intolerable side effect acceptability ratings by patient, OR the experience of an intolerable event as defined above. The escalation of dosing will be as noted in Figure 2 and is based on a modified Fibonacci sequence[101,102] with smaller proportional increases in dose in the escalation scheme. Escalations occur until 2 in a cohort of 3 to 6 experiences DLT (i.e., until ≥33% of patients experience DLT at that dose). The dose **below** this level estimates the MTD.

Participants will be classified as having had a DLT if any of the following conditions are met:

- Persisting (i.e., unresolved after 3 consecutive measurements within a 15-minute interval) hemodynamic side effects defined as below and despite treatments or minimizing infusion rates as specified.
  - Systolic blood pressure <80 or >160
  - Heart rate <40 or >120
- Complete infusion cessation due to intolerable side effect acceptability ratings by patient

Primary Outcomes will be measured at a minimum of every 4-hours from the start of the ketamine infusion (t = 0) for 24-hours (12-hours post infusion cessation). Additional assessments will be administered between the 4-hour measurements if any adverse event or side effect is noted by the patient.

3.4.2 Secondary Endpoints

Patient-reported ***side effect*** acceptability ratings, defined below

Peripartum pain scores, defined in Appendix 1

Peripartum depression scores, defined by Edinburgh Postnatal Depression Score (EPDS)

Side Effect Acceptability Ratings
Any reported side effects are rated by patients. Patient reported side effects (i.e., dizziness, lightheadedness, bad dreams, nausea, vomiting, itchiness, and hallucinations: all dichotomous outcomes) will be evaluated based on patient-specific reports of how "acceptable" or "unacceptable" the side effects are for continued or future use of the study medication. Patient-reported acceptability is defined based on theoretical framework of acceptability[103] and focused on constructs of Burden ("Would experiencing side effects keep you from participating in this intervention (ketamine) again?" yes/no) and Affective Attitude ("Based on your experience with this medication, would you be willing to participate in this intervention (ketamine) again?" yes/no).

1. Acceptability is the absence of patient-centered unacceptable side effects. Patients with side effects who report that the side effects were "acceptable" on digital diary will be counted as having confirmed **side effect** acceptability ratings, regardless of the presence of any side effects to the ketamine dose. Patient-reported acceptability is defined as a "yes" to Affective Attitude with a "no" to Burden.
2. Unacceptability is any patient report of unacceptable side effects, defined as any positive response on the digital side effect diary rated unacceptable by the patient. Either a negative response to Attitude, or a positive response to Burden, will define patient unacceptability.

4 Research Design

This is an open-label maximum tolerated dose (MTD) 3+3 design.[101,102]

Protocol Overview.
Patients will respond to surveys prior to and following cesarean delivery regarding their current pain and mood. Patients will begin study procedures in the third trimester of pregnancy, within approximately one week of scheduled cesarean delivery, until 12-weeks postpartum.

Preoperative weight and vital signs will be measured, and baseline inventories completed (Figure 1; refer to section 1.1). After delivery, cord clamping and declaration of clinical stability by the anesthesiologist (typically~5-15 min after delivery; ±30 minutes), a loading infusion of ketamine 0.05 mg/kg/hour will begin for the first 3-patients in the study. Vital signs and side effect symptomology will be measured 15, 30, and 60 minutes (±5 minutes) after infusion start, and at 4, 8, 10, 12, 16, and 24 hours (±30 minutes) after infusion start. Plasma samples will be collected at 1, 6, 10, and 12 hours (±30 minutes) after infusion. Any report of adverse events or side effects will trigger a blood draw for analysis and correlation of these symptoms to plasma levels of ketamine within the 12-hour infusion. All assessments have been timed to coincide with timing intervals of typical post-CD clinical care interventions. Patients dosing after the first three patients will proceed based on the MTD protocol in Figure 2; refer to section 1.1.

MTD dosing protocol.

A loading dose and maintenance infusion strategy will be used (Figure 2; in section 1.1). MTD to be tested will focus on the initial loading dose used to achieve a higher plasma concentration in a brief period. Ketamine dose will not exceed sub-anesthetic ranges (≤0.2mg/kg/hr[78]). The maintenance rate of 0.05mg/kg/hr is based on our preliminary data suggesting tolerability, and on data suggesting that this rate might yield adequate plasma concentrations necessary for the treatment of depression. The first set of 3 patients will receive a loading infusion of ketamine 0.05 mg/kg/hr for the first data. The decision to escalate the loading infusion dose, enter 3 more at the same level, or stop, will not occur until 3 patients complete the 0.05 mg/kg/hr protocol. A **DLT** event is defined in section 3.4.1.

5 Human Subjects

5.1 Subject Population

The maximum tolerated dose (MTD) 3+3 design encompasses blocks of 3 patients allocated to dosing schematics. In this study, we have 4 dosing schematics to be tested. Therefore, a minimum number of 6 and maximum number of 12 patients will participate in this trial.

5.2 Inclusion Criteria

- Cesarean delivery
- Adults 18 years and older
- Term delivery ≥ 37 weeks gestation anticipated at time of delivery
- ASA PS 2 or 3
-
-
- One of the following must be met for inclusion:
    - Not planning to breastfeed
    - Ketamine use indicated for pain management plan.

5.3 Exclusion Criteria

- Patient going under general anesthesia for cesarean delivery
- Allergy to study medication (ketamine)
- ASA PS 4 +
- Contraindications to neuraxial anesthesia
- Preterm delivery (<37 weeks gestation)
- Anticipated fetal-neonatal complex care plan as indicated in the patient's chart
- Patient history of ketamine or PCP abuse
- Patient history of schizophrenia or psychosis
- Patient history of liver or renal insufficiency
- Patient history of uncontrolled hypertension, chest pain, arrhythmia, head trauma, or intracranial hypertension, uncontrolled thyroid disease, or other contraindications to ketamine
- Participating in another pain intervention trial

- Pre-eclampsia with severe features
- Hemodynamic instability
- Contraindicated medications use:
    - Oral antihypertensive medications (exclusion: hypertensive disorders of pregnancy)
    - Intravenous magnesium (exclusion: pre-eclampsia with severe features)
    - Ketamine, phencyclidine, psilocybins, or any other psychedelics (exclusion: ketamine or PCP abuse)
    - Lithium, valproate, carbamazepine, lamotrigine, haloperidol, chlorpromazine, fluphenazine, aripiprazole, clozapine, or other typical or atypical
    - antipsychotic medications (exclusion: schizophrenia or psychosis)

5.4 Recruitment Methods

The current process for research recruitment is that the research anesthesia team will review charts for all patients presenting for cesarean delivery or who are likely to present for a cesarean delivery in the labor and delivery rooms. Prenatal records will indicate patients planning not to breastfeed. During prenatal anesthesiology evaluations, the anesthesiology team will identify patients who are including ketamine infusion as part of their pain management care. Research staff will contact patients to explain the availability of the study to the patient meeting eligibility criteria.

Additional methods of recruitment include directly approaching potential subjects (in-person), the use of Email/Listserv/Electronic Mailing List, use of Flyers/Posters or Brochures in provider offices and clinics, use of Pitt+Me university research registry portal, and patient/participant referrals.

Patients will be eligible if they are receiving ketamine as part of their clinical care, and these typically include patients with a history of complex pain, history of chronic pain with or without treatment, current everyday smokers, patients with opioid or substance use disorder, and patients who have a documented history of treated or untreated anxiety, depression, or trauma.

Eligible patients will be notified of their eligibility to participate in the study by clinical and research staff. Should the patient wish to hear more, the study coordinator will discuss study participation. Questions will be answered, and time will be afforded to patients per the Informed Consent Procedures outlined, to minimize risks of coercion or undue influence.

Upon completion of the baseline inventories and the ketamine infusion and blood collection, patients will receive a payment of $750 (see Appendix 4 for payment details). Upon completion of the postpartum weekly surveys, payments of up to $150 will be made at both 6- and 12-weeks postpartum.

In-Hospital Encounter
Baseline inventories

Complete infusion and all blood draws	$ 750.00
Postpartum Encounters	
Complete all weekly surveys @ $25.00/week	
Complete weekly surveys for 6 weeks	up to $150.00
Complete weekly surveys for weeks 7-12	up to $150.00
Grand Total	**$ 1,050.00**

5.5 Screen Failures

Participants who are consented to participate in the third trimester of pregnancy, may be withdrawn from the study protocol before, during, or following the cesarean surgery if events arise such as to preclude them from participating in the remainder of the study. These participants will be considered "Screening Failures". The following list is non-comprehensive, but represents the most likely scenarios:

- Vaginal or non-cesarean delivery
- Development of exclusion-based criteria prior to cesarean surgery (i.e., severe preeclampsia, preterm delivery, NICU assessment likely, etc.)
- Severe complications during labor and/or delivery whereby the PI and/or patient's surgeon recommend a change in therapeutic response.

Withdrawn participants will be replaced at a proportion of 1:1. Procedures are as follows:

- Study personnel and investigators will be notified.
- Written documentation of withdrawal and reason for withdrawal will be noted per IRB protocol.
- Study personnel, investigators, and pharmacy will be informed of the need for replacement of pharmaceuticals due to participant withdrawal.
- Subsequent data to be collected from the withdrawn participant will be restricted to the minimum amount necessary to continue to monitor safety, i.e., side effect diary including questions of sedation, LSD short form, dizziness, lightheadedness, bad dreams, nausea, vomiting, pruritus, hallucinations.

6 Study Drug

Ketalar (Ketamine) (C13H16ClNO, 2-(2-chlorophenyl)-2-(methylamino) cyclohexan-1-one) is a cyclohexanone derivative with known analgesic and anesthetic properties. It inhibits biogenic amine uptake, binds opioid receptors, and inhibits N-methyl D-aspartate (NMDA) receptors.

Ketamine will be used for post-cesarean delivery analgesia. Specifically, it will be evaluated for its role in pain reduction, opioid reduction, and improved pain outcomes. In the non-obstetric surgical population, modalities such as intravenous ketamine are well-recognized as effective adjuncts in opioid-reduction strategies for postoperative pain. Ketamine is used off-label as standard clinical care in perioperative pain management for patients with a history of complex pain such as people with chronic

pain (treated or untreated), a history of or current symptoms of depression and anxiety, current smokers, and women with opioid or substance use disorders.

Ketamine is an approved drug or biologic being evaluated for a new indication, population, route of administration, or dosage level not specified in the FDA approved labeling.

6.1 Dose Selection

Safety and Efficacy: Preclinical studies, including studies on animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide reassuring data on minimal potential risks to postpartum women. *[45 CFR 46.204 (a)*]. The selected reference list below demonstrates experience with this drug in dosing regimens matching or exceeding the currently proposed dosing, in both pregnant and postpartum people. The data support low risks to this population. In the dosing regimen that we describe which is "sub-anesthetic" (i.e., ≤0.2 mg/kg/hr, lower than the anesthetic dosing regimens), we expect that the risks are sufficiently low to justify studying it in this fashion.

Selected Relevant References

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6.2 Study Drug Preparation and Dispensing

The study drug, ketamine, will be sourced by investigational (IDS) Pharmacy at UPMC Magee Women's Hospital. The infusions will be packaged and labeled for use in the clinical research study per pharmacy protocols and guidelines. Ketamine will be prepared by pharmacy with dosing instructions. There will be no blinding.

For on-site preparation and dispensing of the study drugs, the following procedures will be followed. The pharmacist of record will: maintain adequate records confirming receipt, expiration dates, or other disposition information on the investigational drug; they will record the name of the individual to whom the drug is shipped, date, quantity, and batch number. They will secure the drug in a locked storage area and monitor to ensure proper storage conditions; they will also complete regular inventory to assure accurate indication of stock on hand, as well as proper recording of stock received, dispensed, and returned. For the patients enrolled for open label pharmacokinetic studies, the pharmacist will generate a label prior to dispensing the study drug, including the date dispensed, quantity and expiration information, drug strength and dose; they will affix the label to the dispensed drug. For dispensing and drug disposition recording, they will record the date dispensed, patient initials or other identifiers, drug treatments, quantity dispensed, initials of dispenser, date and amount of patient returns documented in study records (i.e., returned drug that cannot be re-dispensed). Filing and all drug documentation will occur within study records, medical records, and logs.

Following the cesarean delivery, the initial drug administration (via IV infusion) will begin 15 minutes (± 30 minutes) after cord clamping and declaration of clinical/ hemodynamic stability by the case anesthesiologist after delivery. The maintenance dose will start 60 min (range: +15min) after the initial loading dose. The infusion will be completely stopped 12 hours after the start of infusion. The same infusion pump will follow the patient throughout the postoperative period for 12 hours until completion of the study drug. No manipulation of the infusion pump will occur by the patient. Adjustments to the rate will be at the discretion of the study team and can be physically made by study personnel qualified and trained in these procedures, or by clinical care providers under direct orders from the study team.

6.3 Dose Delays and Modifications

All subjects will be monitored for adverse events throughout participation in this trial. Events requiring a dose delay or adjustment are described below.

Adverse Event, Dose Delays or Adjustments Procedures.
Contingency for lowest dose not tolerated. Our preliminary data suggests that only 1/8 (12.5%) of individuals received an infusion rate lower than 0.05mg/kg/hr due to side effects. However, these data are not representative of our study population, so it is conceivable that PK or PD for side effects may differ in the immediate postpartum setting, and that the lowest loading dose may not be tolerated. If loading dose of 0.05mg/kg/hr is not tolerated, we will follow the dose adjustments in Table 1 and Figure 3 below.

Events that Trigger Dose Adjustment Procedures:

- Persisting unresolved hemodynamic side effects defined as Systolic blood pressure <80 or >160, Heart rate <40 or >120[33]
    - Unresolved after 3 consecutive measurements within a 15-minute interval
- Persisting (i.e., unresolved within 1 hour of onset) side effects sedation, dizziness, lightheadedness, persistent itchiness, bad dreams, hallucinations, or other side effects **that are reported as not acceptable** to patients or clinicians, despite minimizing infusion rate.
- Table 1 includes procedures for dose adjustments.

Patient Reported Side Effects Dose Delays or Adjustments

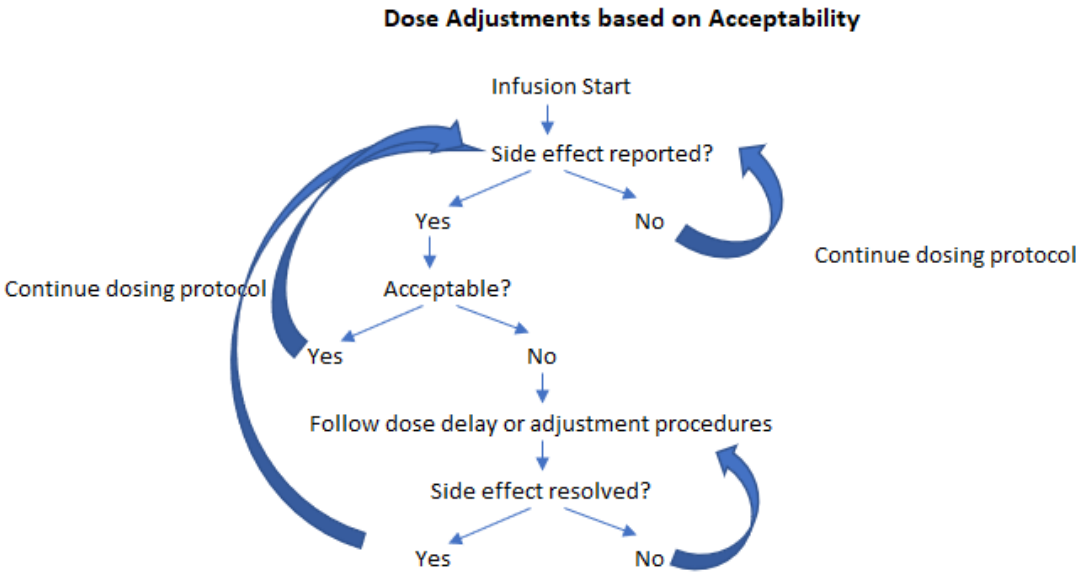
- Side Effect Acceptability ratings are defined in section 3.4.2. Patient reported side effects (i.e., dizziness, lightheadedness, bad dreams, nausea, vomiting, itchiness, and hallucinations: all are dichotomous outcomes). These side effects will be evaluated based on patient-specific reports of how "acceptable" or "unacceptable." Patients reporting side effects and rating them as "unacceptable" will follow the dose delay or adjustment described in the Table 1. If side effects are rated "acceptable" then no dose delays or adjustments will occur.
- Figure 3 Decision Chart for Acceptability Based dose revisions.

Table 1. Loading and Maintenance Dose Adjustment Procedures:

Event	**1st Action**	**2nd Action**		**3rd Action**		**If event does not resolve**
		If event does not resolve	**If the event resolves**	**If event does not resolve**	**If the event resolves**	
Systolic blood pressure <80 or >160, Heart rate <40 or >120	Treat with labetalol or hydralazine per managing anesthesiologist Monitor for 5 minutes for symptom resolution	Hold infusion for 5 minutes - symptom recheck at 5 minutes	↓ dose by 50% (e.g., 0.05mg/kg/hr reduced to 0.025 mg/kg/hr) and continue infusion.	Hold infusion for 5 minutes - symptom recheck at 5 minutes: May D/C infusion based on investigator discretion and monitor subject for safety as described in Section 7.4 and 7.5	↓ dose by 50% (e.g., 0.025mg/kg/hr reduced to 0.013 mg/kg/hr) and continue infusion.	Total of 15 minutes of unresolved hemodynamic effect: D/C infusion and monitor subject for safety as described in Section 7.4 and 7.5 Event qualifies as DLT

Event	1st Action	2nd Action		3rd Action		If event does not resolve
		If event does not resolve	If the event resolves	If event does not resolve	If the event resolves	
If RASS -2 or below, OR Respiratory Rate is < 8	Hold infusion for 10 minutes - symptom recheck every 10 min until resolution	If no resolution within 1 hour: D/C infusion based on investigator discretion and monitor subject for safety as described in Section 7.4 and 7.5	↓ dose by 50% (e.g., 0.05mg/kg/hr reduced to 0.025 mg/kg/hr) and continue infusion.	If no resolution within 1 hour: D/C infusion based on investigator discretion and monitor subject for safety as described in Section 7.4 and 7.5	↓ dose by 50% (e.g., 0.025mg/kg/hr reduced to 0.013 mg/kg/hr) and continue infusion.	D/C infusion and monitor subject for safety as described in Section 7.4 and 7.5 Event qualifies as DLT
Dizziness, lightheadedness, bad dreams, persistent itchiness, hallucinations, nausea, vomiting, or other side effects rated by patient as Not Acceptable	Hold infusion for 10 minutes - symptom recheck every 10 min until resolution Supportive care medications in 9.1	If no resolution within 1 hour: D/C infusion based on investigator discretion and monitor subject for safety as described in Section 7.4 and 7.5	↓ dose by 50% (e.g., 0.05mg/kg/hr reduced to 0.025 mg/kg/hr) and continue infusion.	If no resolution within 1 hour: D/C infusion based on investigator discretion and monitor subject for safety as described in Section 7.4 and 7.5	↓ dose by 50% (e.g., 0.025mg/kg/hr reduced to 0.013 mg/kg/hr) and continue infusion.	D/C infusion and monitor subject for safety as described in Section 7.4 and 7.5 Event qualifies as DLT
Nausea or Vomiting	Rescue medications as indicated in 6.6 Re-evaluate for symptom resolution 10 min after rescue medication Hold infusion for 10 minutes - symptom recheck every 10 min until resolution	If no resolution within 1 hour: D/C infusion based on investigator discretion and monitor subject for safety as described in Section 7.4 and 7.5	↓ dose by 50% (e.g., 0.05mg/kg/hr reduced to 0.025 mg/kg/hr) and continue infusion.	If no resolution within 1 hour: D/C infusion based on investigator discretion and monitor subject for safety as described in Section 7.4 and 7.5	↓ dose by 50% (e.g., 0.025mg/kg/hr reduced to 0.013 mg/kg/hr) and continue infusion.	D/C infusion and monitor subject for safety as described in Section 7.4 and 7.5 Event qualifies as DLT

Figure 3. Dose adjustments based on patient-reported acceptability



6.4 Study Drug Storage and Accountability

For on-site preparation and dispensing of the study drugs, the following procedures will be followed. The investigational drug (IDS) pharmacist of record will: maintain adequate records confirming receipt, expiration dates, or other disposition information on the investigational drug; they will record the name of the individual to whom the drug is shipped, date, quantity, and batch number. They will secure the drug in a locked storage area and monitor to ensure proper storage conditions; they will also complete regular inventory to assure accurate indication of stock on hand, as well as proper recording of stock received, dispensed, and returned. For the 24 patients enrolled for open label pharmacokinetic studies, the pharmacist will generate a label prior to dispensing the study drug, including the date dispensed, quantity and expiration information, drug strength and dose; they will affix the label to the dispensed drug. Pharmacist will generate a label prior to dispensing the study drug, including the date dispensed, quantity and expiration information; they will affix the label to the dispensed drug; they will record but not disclose on the label the drug strength and dose. For dispensing and drug disposition recording,

they will record the date dispensed, patient initials or other identifiers, drug treatments, quantity dispensed, initials of dispenser, date and amount of patient returns documented in study records (i.e., returned drug that cannot be re-dispensed). Filing and all drug documentation will occur within study records and IDS logs. During the infusion, the ketamine will be stored in a lockbox and all Magee standard of care procedures for the safety of controlled substances will be in place for the use of ketamine from the start of infusion through the end of the infusion in the postpartum unit.

6.5 Prohibited Medications

Medications that will not be permitted prior to or during subject participation in the study are as follows:

- Oral antihypertensive medications (exclusion: hypertensive disorders of pregnancy)
- Intravenous magnesium (exclusion: pre-eclampsia with severe features)
- Ketamine, phencyclidine, psilocybins, or any other psychedelics (exclusion: ketamine or PCP abuse)
- Lithium, valproate, carbamazepine, lamotrigine, haloperidol, chlorpromazine, fluphenazine, aripiprazole, clozapine, or other typical or atypical antipsychotic medications (exclusion: schizophrenia or psychosis)

6.6 Rescue Medications

Rescue antiemetics will be provided for patients reporting nausea or vomiting. The following medications will be used to treat nausea or vomiting at the time of patient reporting these symptoms:

- Ondansetron 4mg IVP p.r.n. nausea or vomiting or
- Dexamethasone 4-6mg IVP p.r.n. nausea or vomiting
- After a total of two doses of ondansetron or dexamethasone, additional rescue antiemetics will be given at the full discretion of anesthesiologist

7 Research Activities

Figure 1 (section 1.1) illustrates all encounters for measurements at the preoperative baseline, during the intraoperative period, ketamine infusion period, in the postpartum hospital stay (or until patient discharge), and the 1- to 12-week assessments of pain and depression. Study procedures will begin at enrollment pre-operatively, continue during the ketamine infusion, and hospital post-operative stay, continue weekly in the postpartum period, and end at 12-weeks postpartum.

Information collected at baseline includes maternal demographic information, prenatal pain and depressive symptomology, concurrent acute pain, and covariables such as demographic characteristics, and perceived stress. EPDS is completed twice, at least 1 week apart, prior to delivery. The baseline measures are repeated weekly in the postpartum period until 12-weeks postpartum.

During the ketamine infusion, blood samples will be taken at 1-, 6-, 10-, & 12-hours post-infusion start, as well as at the time of any adverse side effect report to assess ketamine/metabolite levels at the time of event.

Baseline (Preoperative) Procedures.

a. **Demographic Data and Medical History.** Demographic data will be collected through self-reported questions through the RedCap interface. Data from the medical record will be extracted and recorded by trained research associates to be entered into the RedCap interface. Individual surveys are transposed into RedCap for ease of patient use either on a tablet or paper when patients are in person, and via text or email-linked surveys for remote responses. Survey measure timepoints are described in the Appendix.
b. **Surveys**. Patient-reported measures will occur by validated instruments delivered by paper, tablet (in hospital), or via Mosio text-based interface with data integration via REDCap. Texting and email will be used via patient-preferred cellular phone numbers and email addresses for 12-weekly postpartum assessments. Each weekly assessment will occur within ±3 days of the weekly postpartum date. Each set of patient-reported REDCap surveys, in total, is expected to last between 15- and 20-minutes, except for the postoperative timepoints which are expected to take less than 15-minutes to complete. Specific surveys and timeline of surveys will be as follows and as indicated in Table 1 and Figure 1.

Intraoperative Procedures: Day of Surgery

Standardized Surgical, Anesthesia and Analgesia Protocols

Surgical personnel role will be recorded (e.g., titles such as private vs faculty obstetricians, resident, or physician assistant). Standardized spinal anesthesia and intraoperative medications will be as follows. Intraoperative medications include current clinical standards of prophylactic phenylephrine infusion to reduce hypotension and related intraoperative nausea/vomiting; ondansetron at the time of delivery for postpartum nausea/vomiting prophylaxis; and ketorolac 15-30 mg at the time of facial closure. Rescue analgesia and antiemetics will follow our existing clinical protocols.

Spinal anesthesia medications: bupivacaine 0.75% 1.6mL with fentanyl 10-15mcg and morphine 100-150mcg.

Co-medications:

- Per clinical routine, prophylactic phenylephrine infusion at 0.5 mcg/kg/min (37.5mL/hr at standard concentrations) will be started at the beginning of spinal anesthesia induction and discontinued at the time of delivery.
- Supplemental vasopressor boluses are delivered at the full discretion of the managing anesthesiology team.
- Ondansetron 4mg IVP for PONV prophylaxis
- Dexamethasone 4mg IVP for PONV prophylaxis unless contraindications
- Acetaminophen 1000mg either orally pre-operatively or IVPB at facial closure

- Ketorolac 15-30mg IVP at facial closure

Rescue intraoperative antiemetic: Ondansetron 4mg IVP as a rescue dose as needed x1 dose; dexamethasone 4-6mg IVP as needed x1 dose; after this, additional rescue antiemetic can be given at the full discretion of the managing anesthesia team.

Postpartum Analgesia Protocol

Postpartum analgesia protocols will be aligned with routine clinical practice at UPMC Magee-Womens Hospital. Specifically, ketorolac 30 mg IV q6h x24 hours (total of 4 doses) will be administered. After all doses of ketorolac have been given, ibuprofen 600mg q6h x24 hours will be delivered, not to be given within 6 hours of ketorolac. Acetaminophen 500-650mg q4h no more than 4000mg q24hr will be given with the first dose given on postoperative day 0. For severe breakthrough pain rated 7-10 on VAS, the Investigator will be called to assess the need to order oxycodone 5-10mg if necessary, as needed for severe breakthrough pain. The Investigator may also assess the need for parenteral rescue agents, namely hydromorphone.

Discharge Analgesia Regimen

Consistent with current routine clinical practice at UPMC Magee, subjects will be discharged with a prescription for oxycodone 5-10mg q6h #12-20 p.r.n. severe pain. Adjustments to this regimen will be made on an individual basis based on prescriber and institutional practice changes that may arise.

Surgical case reports.

Surgical elements will be collected from surgeons as well as data abstraction from the medical record (Table 3). Surgeons will complete the Surgeon Operative Survey (Table 2) described below:

Table 2. Surgical Operative Survey

Surgeon/Obstetrician Operative Survey
1. Reason for Cesarean Delivery
2. Type of Skin Incision
3. Type of Uterine Incision
4. Dissection type and inclusion of rectus
5. Uterine exteriorization
6. Bladder Flap
7. Any unanticipated surgical challenges?
8. Please rate difficulty of delivery (0-10 numeric rating scale, 0 is no difficulty, 10 is the most difficult imaginable)
9. Please rate difficulty of overall surgery (0-10 numeric rating scale, 0 is no difficulty, 10 is the most difficult imaginable)
10. Please rate degree of adhesive disease (0-10 numeric rating scale, 0 is no adhesive disease, 10 is the most adhesive disease imaginable)
11. Please rate degree of difficulty of fetal extraction. (0-10 numeric rating scale, 0 is no adhesive disease, 10 is the most adhesive disease imaginable)
12. Were there any unanticipated surgical challenges encountered? (yes/no)
13. Did you make any intraoperative consultations to other surgeons? (yes/no)
14. What materials were used for Facial and Skin closure.

Table 3. Surgical data abstraction from the medical record

Element	Where to find in EHR
Duration of surgery (min)	Cerner Surginet Operative Report
Surgical assist role (resident, physician assistant)	Cerner Surginet Operative Report
Surgical attending role (private vs faculty)	Cerner Surginet Operative Report
Infant weight (grams)	Cerner Surginet Operative Report
Apgar score 1 minute (integer 0-9)	Cerner Surginet Operative Report
Apgar score 5 minutes (integer 0-9)	Cerner Surginet Operative Report
Estimated blood loss (mL)	Cerner Surginet Operative Report Cerner SA Anesthesia Record
Total intravenous fluids administered (mL)	Cerner SA Anesthesia Record
Total urine output (mL)	Cerner SA Anesthesia Record
MME Opioid use in postpartum days 1-3	Cerner SA Anesthesia Record

Ketamine Infusion, Side Effect Measures, and Plasma Sampling Procedures.

Preoperative weight and vital signs will be measured, and baseline inventories completed (Figure 1). After delivery, cord clamping and declaration of clinical stability by the anesthesiologist (approximately 5-15 minutes after delivery, ± 30 minutes), a loading infusion of ketamine 0.05 mg/kg/hr will begin for the first 3-patients in the study. Vital signs and Richmond Agitation Sedation Scale (RASS), and self-reports of side effects will be measured 15, 30, and 60 minutes (±10 minutes) after infusion start, and at 4- 8- 10- 12- 16- 24- hours (±30 minutes) after infusion start. Plasma samples will be collected at 1- 6-, 10- and 12- hours (±30 minutes) after infusion start via an indwelling IV catheter to facilitate ease of access. Plasma samples at 1- 6-, 10- and 12- hours after infusion start will be used to calculate Cmax, AUC, and Css and to correlate DLTs with these PK parameters. Any report of adverse events or side effects will trigger a blood draw for analysis and correlation of these symptoms to plasma levels of ketamine. All assessments have been timed to coincide with timing intervals of typical post-CD clinical care interventions. Patient dosing after the first three patients will proceed based on the MTD protocol in Section 1.1.

MTD Dose Adjustment Procedures.

Figure 2 (section 1.1) outlines the dosing approach. Dose adjustment procedures are outlined in section 6.3.

Side Effect Acceptability Ratings.

Our existing and previously tested **digital diary** will automate alerts for questions about side effects after infusion start at 15-, 30-, 60- minutes, and every 4 hours in the first 24 hours after infusion start (Figure 1, section 1.1). The diary has been tested and used by our group in previous work; alerts coincide with RASS assessments and similar timing of clinical assessments for routine CD nursing care and monitoring (i.e., is not more burdensome or intrusive to patients than routine clinical post-CD care). The digital diary will assess side effects

(i.e., dizziness, lightheadedness, bad dreams, nausea, vomiting, itchiness, and hallucinations: all dichotomous outcomes). Any positive response to any item will trigger the subject to rate their acceptability of side effects in the following way. Patient-reported acceptability is defined based on theoretical framework of acceptability[103] and focused on constructs of *Burden* ("Would experiencing side effects keep you from participating in this intervention (ketamine) again?" yes/no) and *Affective Attitude* ("Based on your experience with this medication, would you be willing to participate in this intervention (ketamine) again?" yes/no). Either a negative response to Attitude, or a positive response to Burden, will define patient unacceptability.

Side Effects.

Monitoring during the infusion will follow our clinical standards of perioperative ketamine monitoring. A maternal side effect digital diary will also be used. The digital diary has been previously developed and tested in our preliminary lactation volunteer study. The diary alerts questions to patients include the Richmond agitation-sedation scale (RASS)[104], dysphoria (LSD short form[105]), and side effects. Automated alerts for abnormal responses go to clinical and research staff for immediate action. Any report of side effects will trigger a blood draw for analysis and correlation to measured plasma levels.

Postpartum 12-week Follow-up Procedures.

Figure 1 (section 1.1) outlines weekly follow-up procedures. Participants will receive weekly surveys containing the questionnaires that are specified in Appendix 1. Surveys focus on pain and depression symptoms throughout the postpartum period.

7.1 Screening Procedures

Per our existing research procedures, patients will be screened from the Magee-Womens Hospital OB surgery schedule by dedicated trained research associates. Screening will be completed using the "Core Surgical PowerChart" and "Epic" Electronic Health Record (EHR) systems. All procedures will follow existing processes with clinicians for patient enrollment in research. Patients scheduled for CD are contacted prior to surgery by phone or in person to assess eligibility, explain the study protocol, and provide consent. Patients who are eligible within the prenatal clinics will be contacted prior to surgery in person, via a MyUPMC message or using videoconferencing to explain the study and obtain consent.

7.2 Study Entry Procedures

Participants will be screened for eligibility prior to consent. Inclusion criteria and exclusion criteria are described in Sections 5.2 and 5.3.

7.3 Study Drug Administration

Following the cesarean delivery, the initial drug administration will be made after cord clamping and once anesthesiologist has declared hemodynamic stability (i.e., infusion starts approximately 5-15 minutes after delivery, ± 30 minutes). The infusion will be completely stopped at 12 hours after the start of infusion. The same infusion pump will follow the patient throughout the postoperative period for 12 hours until completion of the study drug. No manipulation of the infusion pump will occur by the

patient. Adjustments to the rate will be at the discretion of the study team and can be physically made by study personnel qualified and trained in these procedures, or by clinical care providers under direct orders from the study team.

7.4 Safety Assessments/Procedures During Treatment

Maternal monitoring during the infusion will follow our clinical standards perioperative ketamine monitoring and the standard Magee system safety precautions for administration of a controlled substance will be in place to protect from any misuse. A licensed and qualified anesthesia provider (resident, fellow, nurse anesthetists, or anesthesiologist) will be present during the first 30 minutes of the infusion and will have the option to treat blood pressures >180/100 mm Hg or heart rate >110 bpm. The study infusion will be discontinued if 3 consecutive measurements within a 15-minute interval remain above protocol-defined limits despite intervention (section 6.3). Maternal side effect symptomology monitoring will occur throughout the ketamine infusion. Automated alerts for maternal side effect responses go to clinical and research staff for immediate action. Any report of side effects will trigger a blood draw for analysis and correlation to measured plasma levels.

An independent DSMB will define frequency of monitoring of tolerability and DLT data. The severity of adverse events are classified in section 10.1

7.5 Safety Assessments/Procedures After Ketamine Infusion Stop

Maternal side effect monitoring following the infusion will continue at 4-hour intervals for 12-hours after the cessation of ketamine infusion. Monitoring will occur via clinical staff monitoring and via patient self-report indices of side effect symptomology (Figure 1; section 1.1).

After the study drug infusion is complete, safety and efficacy assessments consist of the following. Digital diaries will assess self-reported side effects according to the study schematic Figure 1; 1.1, until 12 hours after infusion discontinuation. Vital signs will be monitored during that same period.

7.6 Safety Assessments/Procedures During Postpartum Surveys

Efficacy assessments, exploratory in nature, will consist of pain and depression symptom screening at regular intervals from one week postpartum until 12 weeks after delivery, according to the time intervals indicated in the study schematic Figure 1; 1.1. Positive screens for depression will be initiate an immediate response to the study team. The protocol for positive depression screens is presented in Appendix 4. All patients who screen positive for depression (EPDS total score > 14 or positive answer to question #10) will be contacted and receive consultation instructions.

After all study procedures are complete 12 weeks after delivery, there will be no further active assessments of safety and efficacy by study staff. Participants will continue to have access to their primary care physicians and emergency services.

8 Potential Risks and Benefits

8.1 Reasonably Foreseeable Risks Related to Study Drug

Common side effects of ketamine are sedation, dizziness, lightheadedness, bad dreams, hallucinations, euphoria, dysphoria, nausea, vomiting. These risks are minimized by using doses below the doses that we typically see these side effects. Seriousness: mild to moderate.

Uncommon effects of ketamine include hypertension or hypotension, tachycardia, or bradycardia. These risks are minimized as much as possible by using doses below the doses that we typically see these effects. If these effects are noted, the drug will be stopped until the effects dissipate. Should the effects not dissipate, the PI will evaluate and determine whether the patient requires additional care. If these uncommon effects are experienced, an SAE log will be completed and the IDSMB and IRB notified. Seriousness: mild to moderate

8.2 Reasonably Foreseeable Risks Related to Research Interventions

Risks to confidentiality. There is a risk of breach of confidentiality with the screening procedures and the collection and storage of personal health information. To protect against this risk, all screening procedures will be done by study staff who have been completely trained in HIPAA/privacy procedures; all data collected will be identifiable only by a unique subject ID number, and no personal identifiers will be stored with the data. Linkage files identifying subjects will be stored only in physical records that are kept in locked files accessible only by study staff; electronic data will be handled and protected whereby any linkages between study ID number and patient identification will be separated, password protected, and stored behind the UPMC firewall. There are some cases in which a researcher is obligated or authorized by law to report mental health symptoms, such as serious threats to public health and safety. For example, if patients indicate that they are in imminent risk of harm (e.g., suicide or serious threats toward the wellbeing of others), the researchers will contact the appropriate authorities to protect patients or the public. Seriousness: mild

Risks of inconvenience from surveys. To minimize the inconvenience/time burden on participants associated with the survey questions, we will use an electronic (email) interface preferentially and will minimize the number of questions to strictly only the number necessary to address important aspects of our study questions. Seriousness: mild

Risk of survey discomfort. An uncommon risk includes inconvenience and potential emotional discomfort are risks associated with answering survey questions. Subjects will be asked to answer questions regarding pain and depression before, during, and after having their babies. Answering these questions may be viewed as an inconvenience. Seriousness: mild

Risks of IV blood collection. Common risks associated with blood collection include bruising or swelling at the collection sight, discomfort during venous blood draw, and infection. Seriousness: mild

Risk of sub-anesthetic ketamine infusion dose titration. Common risks include nausea, euphoria, dizziness, or lightheadedness. Seriousness: mild. Uncommon risks include temporary hypertensive event.

Seriousness: mild to moderate; uncommon risks include hallucinations or dysphoria. Seriousness: mild to moderate.

8.3 Potential Benefits

The potential direct benefits to subject participation in this study is enhanced pain control, opioid reduction, closer follow-up for depression symptoms, and reduced depression risk. There are societal benefits in that there will be increased knowledge about the use of ketamine after birth to reduce depression, alleviate pain and decrease opioid use. Ultimately, the results of this study, if significant, will enable health care providers to improve the health of mothers.

9 Protection Against Risks

9.1 Management of drug related toxicity

The PI is a practicing, board-certified clinical anesthesiologist with extensive experience in the administration of this study drug under normal clinical circumstances. The study drug will be started during routine anesthesia care where monitoring is the strictest and closest, thereby enabling early detection of any safety events. The patients will remain monitored in an appropriate care environment throughout the duration of the 12-hour drug infusion, enabling timely detection and treatment of any serious events should they occur. Staff will also be trained to be familiar with common and uncommon side/adverse events for reporting.

Supportive care drugs that may be used in the event of drug related toxicity:

- Event: Persisting unresolved hemodynamic side effects defined as Systolic blood pressure <80 or >160, heart rate <40 or >120, unresolved after 3 consecutive measurements within a 15-minute interval
    - Supportive care medications:
    - Labetalol 10-20mg IVP or Hydralazine 10-25mg IVP p.r.n. hypertension at discretion of managing anesthesiologist.
- Event: Persisting side effects sedation, dizziness, lightheadedness, bad dreams, hallucinations, or other side effects that are reported as not acceptable to patient or clinicians, despite minimizing infusion rate
    - Supportive care medications:
    - Midazolam 1-4mg IVP p.r.n. dysphoria, at discretion of managing anesthesiologist.

Refer to Section 6.8 for Rescue Drugs.

Refer to Section 6.3 of the protocol for instructions on dose delays and modifications.

9.2 Management of research related risks

All research interventions/activities will be conducted in private patient care areas. The collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is collected.

All demographic and clinical information about the subject will be stored in an electronic password-guarded study database under the supervision of the Investigator for this protocol. The electronic system REDCap has features that can enable its use as certifiably compliant with the DFTA regulations at 21 CFR part 11 but due to the limited scope of this clinical research study, the electronic data recording system has not been certified as fully compliant. The data will be stripped of individual identifiers at the time of analysis and stored anonymously with a subject number. Information linking subject identifiers with the coded subject number will be stored under password proection on computers in locked areas, with access to the database manager. Access to the database will be limited to the data manager and staff under the supervision of the Investigator.

All staff involved in this study are properly credentialed and instructed in the areas of testing, confidentiality, and safety. All study team members will be properly trained on protocol requirements, trained in HIPAA/privacy procedures, and GCPs. Research procedures performed for study purposes will be performed by qualified individuals as evidenced by education, experience, and/or training. All members of the study team will have the required human subjects and confidentiality training, which includes information about maintaining data integrity and security. Confidentiality will be guarded using established procedures such as storing data in locked cabinets within locked offices or locked data rooms, coding CRFs and research specimens by study identification numbers rather than any personal identifying information to avoid revealing the identity of subjects, and aggregating data across participants. The key linking names and study identification numbers will be kept separately from the data sets with limited access by study personnel. Only study personnel will have access to the data sets on protected servers.

The Investigator will retain the data for the entire period of this study and will retain the specified records and reports for up to seven years after the study's publication. The Investigator may continue to use and disclose subjects' de-identified information for the purpose of this study for a minimum of seven years after final reporting or publication of the study. If the subject and/or legal representative decide to withdraw or be withdrawn from study participation, they may request in writing that the study data and samples be destroyed. Subject names or other directly identifiable information will not appear on any reports, publications, or other disclosures of clinical study outcomes.

Clinical data recorded on the electronic database will include intraoperative obstetrician case report forms completed by the obstetrician at the end of surgery, and hospital postpartum morphine equivalent dosing.

10 Adverse Events and Serious Adverse Events

The proposed clinical trial will use the FDA definition of an adverse event (AE). Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether considered drug related.

The proposed clinical trial will use the FDA definition of SAE. A serious adverse event is any untoward clinical event that is thought by either the investigator or the sponsor to be *unexpected and at least possibly related* to the study and results in any of the following:

1. Death
2. A life-threatening adverse event
3. Inpatient hospitalization or prolongation of an existing hospitalization
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly or birth defect
6. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient, or subject, and may require medical, or surgical intervention to prevent one of the serious outcomes listed above.

Adverse events will be assessed on each participant at stated intervals in Figure 2 section 1.1, both during infusion, and for 12 hours after infusion discontinuation. Duration of monitoring is based on known pharmacokinetics of ketamine.

When an adverse event is discovered, the event will be assessed for severity, relatedness, and expectedness. All adverse events will be documented in the research records and followed until resolved or back to baseline grade.

10.1 Severity

The severity of adverse changes in physical signs or symptoms will be classified as follows:

- ***Grade 1 (Mild):*** asymptomatic or mild symptoms; clinical or diagnostic observation only; intervention not indicated.
    - e.g., sedation, dizziness, lightheadedness, bad dreams, hallucinations, euphoria, dysphoria, nausea, vomiting
- ***Grade 2 (Moderate):*** minimal, local, or noninvasive intervention indicated; limiting age-appropriate ADL.
    - e.g., dysphoria, vomiting
- ***Grade 3 (Severe):*** medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care/ADL.
    - e.g., hypertensive urgency or emergency requiring escalated or inpatient treatment
- ***Grade 4 (Life-threatening):*** consequences; urgent intervention indicated.
    - e.g., stroke from uncorrected severe hypertension

- ***Grade 5 (Death):*** event is a direct cause of death.

An independent DSMB will define frequency of monitoring of the tolerability and DLT data.

10.2 Relatedness

Adverse Events and Serious Adverse Events will be subject to the following criteria to determine the relatedness of the experienced event to the research study, protocol, and/or drug.

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug is clinically plausible. The event must be pharmacologically or phenomenologically definitive.

- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals and follows a clinically reasonable response on withdrawal of the study drug.

- Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study 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 whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- Not Related – The AE is completely independent of study intervention administration, and/or evidence exists that the event is related to another etiology. There will be an alternative, definitive etiology documented by the clinician.

10.3 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 information previously described (sections 8.2 and 9.1). Note that the risks listed in Section 8.1 are considered expected and would <u>not</u> require reporting *unless* the frequency or severity is greater than expected. Events not listed in Section 8.1 but that are listed in the FDA-approved package insert, should

also be considered expected. In such cases, depending on the nature and severity of the event, an amendment may be necessary to add the risk to Section 8.1 and the consent form document.

10.4 Reporting Serious Adverse Events

If there is a suggestion that any research procedures have resulted in an injury to subjects, there will be immediate contact with the Principal Investigator who is listed on the first page of the informed consent documents. Any SAE, which is determined by the PI to be unexpected and at least possibly related to study intervention, will be reported to the IRB as soon as possible. The PI is responsible for notifying the FDA within required timeframes. The IDSMB will be notified in writing at the soonest possible timepoint that the event has been identified. The IRB and FDA and will include all known details regarding the nature of the SAE. Outcomes of SAEs not previously reported will be reported to the PI, IRB and FDA via a follow-up report.

Life-threatening or fatal unexpected adverse events associated with the use of the study drug or procedures must be reported to the IRB within 24 hours of discovery of the incident with subsequent follow-up submission of a detailed written report. The IDSMB and IRB will be notified by telephone or facsimile transmission of a human adverse event that is fatal or life-threatening no later than 7 calendar days after receiving the respective human adverse event information, followed by the subsequent submission of a written IND Safety Report. Serious and unexpected adverse events associated with the use of the study drug or procedures will be reported to the IRB with subsequent follow-up submission of a detailed written report in accordance with the respective policies and procedures of the IRB. A summary report of the findings will be prepared and submitted to the regulatory agencies. A written IND Safety Report (i.e., Form FDA 3500A) will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the investigator-sponsor's receipt of the respective adverse event information.

A summary of the SAEs that occurred during the previous year will be included in the FDA annual progress report as well as in the annual IRB continuing review.

11 Withdrawal of Subjects and Stopping Rules

This section outlines the criteria that specify when dosing an individual subject, cohort, or trial will be suspended.

11.1 Adverse Events Requiring Discontinuation

For this study, a serious adverse event is any untoward clinical event that is thought by either the investigator or the sponsor to be related to the study and results in any of the following outcomes:

1. Death
2. A life-threatening adverse event
3. Inpatient hospitalization or prolongation of an existing hospitalization

4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. A congenital anomaly or birth defect
6. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient, or subject, and may require medical, or surgical intervention to prevent one of the serious outcomes listed above.

If clinically important and unexpected adverse experiences or clinically important study-related adverse experiences occur, they will be recorded on the adverse event case report form.

Adverse Events Reporting Timeline is documented in 10.4.

Withdrawal of Subjects due to Adverse Events

Participants will be withdrawn if they experience a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or other important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient, or subject, and may require medical, or surgical intervention to prevent one of the serious outcomes listed above.

DSMB will review all events pertaining to participant withdrawals. An independent decision will be made regarding trial discontinuation based on risk assessment for current and future trial participants.

Withdrawn participants will be replaced at a proportion of 1:1. Procedures are as follows:

- Study personnel, investigators, and pharmacy will be informed of the need for replacement due to participant withdrawal.
- Subsequent data to be collected from the withdrawn participant will be restricted to the minimum amount necessary to continue to monitor safety, i.e., side effect diary including questions of sedation, LSD short form, dizziness, lightheadedness, bad dreams, nausea, vomiting, pruritus, hallucinations.

11.2 Other Criteria Requiring Discontinuation

Withdrawal of Subjects for reasons other than Non-compliance or Adverse Events:

- Protocol non-adherence: incorrect dosing strategy or other non-adherence points at the judgement of the PI
- Incomplete side effect diary data, defined as missing 20% or more responses

Withdrawn participants will be replaced at a proportion of 1:1. Procedures are as follows:

- Study personnel, investigators, DSMB will be informed of the need for replacement due to participant withdrawal.

- Subsequent data to be collected from the withdrawn participant will be restricted to the minimum amount necessary to continue to monitor safety, i.e., side effect diary including questions of sedation, LSD short form, dizziness, lightheadedness, bad dreams, nausea, vomiting, pruritus, hallucinations.

11.3 Clinical Trial Stopping Rules

This study may be suspended, or prematurely terminated if there is sufficient reasonable cause. DSMB will review all events pertaining to participant withdrawals. An independent decision will be made regarding trial discontinuation based on risk assessment for current and future trial participants.

Written notification, documenting the reason for study suspension or termination, will be provided by the suspending, or terminating party to study participants, investigators, funding agency, the IND sponsor, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule.

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

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

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

12 Statistical Analysis

By virtue of its design, the maximum tolerated dose (MTD) 3+3 design encompasses a minimum number of 6 and maximum number of 12 patients enrolled in this trial. The results identify the drug dose at which ≥33% of patients experience dose limiting toxicity, which we have defined by unacceptable side effects or adverse events. The number of subjects at each dose is dictated by traditional MTD 3+3 design, balancing the risks associated with the study drug and the assessment of adverse event rates. A formal power calculation was not performed.

12.1 General Approach

The outcome of this design is the determination of the Maximum Tolerable Dose of ketamine infusion post-cesarean delivery. As such, the final dosing of the MTD design is the primary outcome determined as patient report of tolerated dose and acceptable side effect experiences in greater than 66% of patients.

12.2 Sample Size Determination

The number of subjects (minimum of 6; maximum of 12) at each dose is dictated by traditional MTD 3+3 design, balancing the risks associated with the study drug and the assessment of adverse event rates. A formal power calculation was not performed.

12.3 Analysis of Primary Endpoint

Maximum Tolerated (Ketamine) Dose (MTD): The MTD will be defined as the dose at which fewer than 33% of patients experience intolerable effects.

Tolerability (dichotomous Yes/No)

- Tolerability (YES) will be defined as: lack of serious adverse events (serious adverse event defined as: severe unresolved hemodynamic effect: systolic blood pressure <80 or >160, heart rate <40 or >120).[33]
- *Lack of Tolerability* will be defined as presence of any serious adverse event (i.e., severe unresolved hemodynamic effect: systolic blood pressure <80 or >160, heart rate <40 or >120).[33]

For this MTD study, rates of the primary endpoint will be reported as numbers and percentages. Rates of blood pressure and heart rate events will be reported as numbers and percentages.

12.4 Analysis of Secondary Endpoints

Side effect acceptability ratings will be reported for each side effect reported as numbers and percentages. Examination of patient pain and depression scores in the 12-weeks post cesarean delivery will be explored. The limited sample size of the MTD design precludes definitive conclusions regarding pain and depression. General linear mixed models will be used to assess trends in pain and depression over the peripartum period according to dose exposure. Paired t-tests may be used to assess changes in pain or depression scores from the preterm to postpartum 12-week assessments.

13 Data and Safety Monitoring

Monitoring of safety and data quality in the proposed study will be the responsibility of all personnel on the project, with primary responsibility and supervision by the Investigator. An Independent Data and Safety Monitoring Board (IDSMB) will be convened prior to initiation of the studies and administrated by the University of Pittsburgh CTSI. The study will be reviewed a minimum of quarterly in the first year and twice yearly on an annual basis (or more frequently as deemed necessary) by the IDSMB. The IDSMB will determine the actual frequency of meetings and monitoring, including convening of emergency meetings when necessary.

The Institutional Review Board (IRB) will approve the Statement of Informed Consent for the study and provide institutional oversight of data and safety issues. The study protocol will be approved by the IRB prior to recruiting or obtaining consent from any participants.

Each participant will sign the Informed Consent Form described above prior to participating in the study. To ensure participant safety, once participants are enrolled in the study, study staff will immediately report any adverse and serious adverse events to one of the Investigators. The Investigator will, per standardized procedures, report them to the IDSMB and IRB for review.

13.1 Data Safety Monitoring Plan

Monitoring of safety and data quality in the proposed study will be the responsibility of all personnel on the project, with primary responsibility and supervision by the Investigator. There will be an evaluation of the progress of the research study, including assessments of data quality, timelines, participant recruitment, accrual, and retention. The Investigator will also review the outcome and adverse event data to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation and whether the study should continue as originally designed or should it be re-evaluated and changed. A summary report of the data and safety monitoring meetings will be provided to the IRB at the time of the continuing review.

Regarding monitoring of data quality and protected health information, all required personnel proposed for this project will have the required human subjects and confidentiality training, which includes information about maintaining data integrity and security. Confidentiality will be guarded using established procedures such as storing data in locked cabinets within locked offices or locked data rooms, electronic data stored behind UPMC/university firewalls and/or use of REDCap with attendant compliance with data safety standards, coding by study identification numbers rather than any personally identifying information to avoid revealing the identity of subjects, and aggregating data across participants. The key linking names and study identification numbers will be kept separately from the data sets with limited access by study personnel. Only study personnel will have access to the data sets on protected servers. Oversight of all aspects of data management will occur with the Investigator.

13.2 Parameters to be Monitored

The following progress will be monitored throughout the course of the research to ensure the safety of subjects as well as the integrity and confidentiality of their data.

- An evaluation of the progress of the research study, including subject recruitment and retention, and an assessment of the timeliness and quality of the data.
- A review of collected data (including adverse events, unanticipated problems, and subject withdrawals) to determine whether there is a change to the anticipated benefit-to-risk assessment of study participation and whether the study should continue as originally designed, should be changed, or should be terminated (see section 10.1).
- An assessment of external factors or relevant information (e.g., pertinent scientific literature reports or therapeutic development, results of related studies) that may have an impact on the safety and study participants or the ethics of the research study.
- A review of study procedures designed to protect the privacy of the research subjects and the confidentiality of their research data.

The severity of adverse changes in physical signs or symptoms were summarized in section 10.1.

13.3 Frequency of Monitoring

The Investigator will review subject safety data as it is generated. The Investigator and the research staff will meet on a weekly interval – and more frequently as necessary – to review data coding and capture, documentation and identification of adverse events, complaints or other issues, and subject confidentiality issues. There will be an evaluation of the progress of the research study, including assessments of data quality, timelines, participant recruitment, accrual, and retention. The PI will also review the outcomes and adverse event data to report to IDSMB who will subsequently decide whether there is any change to the anticipated benefit-to-risk ratio of study participation and whether the study should continue as originally designed or should it be re-evaluated and changed.

An Independent Data and Safety Monitoring Board (IDSMB) will be convened prior to initiation of the studies and administrated by the University of Pittsburgh CTSI. The study will be reviewed a minimum of quarterly in the first year and twice yearly on an annual basis (or more frequently as deemed necessary) by the IDSMB. The IDSMB will determine the actual frequency of monitoring meetings, including convening of emergency meetings when necessary.

13.4 Clinical Monitoring

In accordance with 21 CFR 312.50 clinical site monitoring will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and that the conduct of the trial is in compliance with current, approved protocol/amendment(s).

13.5 Data and Safety Monitoring Board

An Independent Data and Safety Monitoring Board (IDSMB) will be convened prior to initiation of the studies and administrated by the University of Pittsburgh CTSI. The IDSMB will include individuals in the specialties of Anesthesiology, Psychiatry, Neonatology, and Perinatology as such to create a comprehensive review of the study protocol and participants. The study will be reviewed a minimum of quarterly in the first year and twice yearly on an annual basis (or more frequently as deemed necessary) by the IDSMB. The IDSMB will determine the actual frequency of meetings and monitoring, including convening of emergency meetings when necessary.

14 Regulatory, Ethical, and Study Oversight

14.1 IRB Approval

The PI will obtain, from the University of Pittsburgh IRB, prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the Investigator will promptly notify the University of Pittsburgh IRB of the deviation.

The IRB will review and approve the Informed Consent Document for the study and provide institutional oversight of data and safety issues. The study protocol will be approved prior to recruiting or obtaining consent from any participants. Moreover, the study will be reviewed at a minimum of annual basis (or more frequently as deemed necessary) by the IRB committee. Each participant will sign the approved Informed Consent Form prior to participating in the study.

The University of Pittsburgh IRB operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable ICH Guidelines on GCP.

14.2 Informed Consent Procedures

Details of Participant Recruitment:
Subjects approached for enrollment in this study are patients being seen during normal clinical care or by study personnel as part of recruitment procedures as follows. Screening will occur by prenatal clinic, or obstetric operating room schedule, or in the labor and delivery suite. After review, potential patients scheduled for elective cesarean delivery will be approached after clinical staff confirm it is appropriate to do so. For scheduled elective cesarean deliveries, participants will be contacted by phone or in person from obstetric clinic, within 0-21 days prior to the scheduled delivery, to disclose eligibility in the study and to assess their desire to speak to the study team to learn more about the study. The anesthesia team will see all patients presenting for cesarean delivery. During this visit, the anesthesia team typically reviews the patient's medical history, explains the anesthetic plan, and obtains consent for anesthesia. In this study, for eligible participants, investigators will also use this visit to explain the availability of the study to the patient meeting eligibility criteria, when the anesthesiology consult occurs. Should the patient wish to hear more, researchers will discuss risks, benefits, and alternatives to study participation. Questions will be answered, and time will be afforded to patients per the Informed consent Procedures outlined below, minimizing risks of coercion or undue influence.

Recruitment will also occur using Pitt+Me (https://pittplusme.org/) and study fliers within the OBGYN clinics at Magee Womens Hospital. Interested individuals will contact the study team directly. Screening

will take place over the phone, and eligible and interested individuals will be approached prior to their standard cesarean delivery care to go through the informed consent process.

Informed Consent Procedures.
The consent process will take place virtually or in person in prenatal clinics or in the preoperative holding area on day of surgery, in accordance with our prior study procedures. The informed consent process will begin when the patient has indicated interest in participating in the study. For women with scheduled cesarean delivery, a phone call with the investigator 0-21 days ahead of time will disclose eligibility and to assess their desire to speak to the study team to learn more about the study. Face-to-face (video and audio) virtual informed consent will be permitted if acceptable to both patient and investigator team, and will follow existing procedures, security and protection protocols that are currently used in our other research protocols.

Patients will be offered additional time to consider the study and their desire to participate - the amount of time for them to consider will be determined by the patient herself and individualized to her level of comfort. They will be informed that they do not need to make any decisions in that encounter and will be encouraged to take time to consider and discuss the study with their support persons without the presence of study personnel. Blank informed consent documents and study brochures will be made available to the subjects and their support people, to support their deliberations.

Individuals will be provided with full explanation of study-related goals and procedures. Questions will be answered for the patient as well as their support people. Patients will be given as much time as they desire to read the consent form and materials and ask questions. If desired, patients can take materials home for review and will be consented to participate via videoconferencing software and electronic consent via REDCap.

Informed consent procedures will be followed and written informed consent will be obtained. No elements of informed consent will be waived.

14.3 Protocol Deviations

Clinical research investigators and staff will be familiarized with the study protocol, GCPs, and applicable federal regulations to ensure that the study protocol procedures are followed. When a deviation is perceived to have occurred, the procedure completed will be verified against the study protocol, applicable regulations and relevant GCP principles. Deviations in the study protocol will be identified verbally and in writing to the PI and/or study coordinator as they occur. In addition to deviations noticed during completion of study protocol procedures, deviations may be identified through routine monitoring visits or audits of the clinical research records, as the research team will meet weekly to review the study recruitment, procedures, and retention. All deviations will be verified and presented to the PI for timely assessment and IRB reporting, if warranted. Any deviation, regardless of severity, will be recorded in the Non-compliance/deviation log by the PI or research staff member as they occur. Protocol deviations that do not meet the definition of IRB reporting requirements will be subject to yearly review and evaluation during the continuing review period.

Deviations determined to be reportable to the IRB include Unanticipated Problems involving risk to participants, Serious Non-compliance with study protocol, and/or Continuing Non-compliance of study protocol. The PI will submit all Unanticipated Problems Involving Risks to Human Subjects or Others and incidents of Reportable Non-compliance within 10 working days of the Investigator becoming aware of the Reportable New Information. *Unanticipated Problems involving risk to participants* include adverse medical occurrences that are:

- Unexpected in terms of nature, severity, or frequency; AND
- Related, or possibly related, to a subject's participation in the research; AND
- Places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Any protocol deviation that results in an Adverse Events which are unexpected, fatal, or life-threatening, and related or possibly Related to the Research Intervention will be immediately reported to the PI, Clinical Research Coordinator, and reported to the IRB within 24 hours of learning of the event. (All other internal Adverse Events that meet the definition of an Unanticipated Problem Involving Risk to Human Subjects or Others will be reported to the IRB within 10 working days of the investigator learning of the event. If an unexpected adverse event occurs, the investigators will reassess the risk to benefit ratio of the study and will submit any modifications necessary to the IRB. At the time of IRB renewal, the PI will submit information about the frequency of monitoring, any relevant information that may influence the safety or ethical conduct of the study, and any conclusions or changes to the study necessary for continuation, modification, or termination of the study.

Reportable incidence of Non-compliance includes any protocol deviation that:

- Significantly adversely affects the safety, rights, or welfare of the research participants; OR
- Significantly compromises the quality or integrity of the research data (i.e., negatively impacts the ability to draw conclusions from the study data); OR
- Represents Continuing Non-compliance (i.e., has been previously reported or represents a pattern of ongoing non-compliance).

I**ncidents of Non-compliance that do not meet the IRB reporting requirements** will be documented in a Non-compliance/deviation log and managed as part of the Data and Safety Monitoring Plan. The Non-compliance/deviation log will be kept throughout the study and the documentation will be made available upon request.

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Appendix 1 – Surveys Measures

Item	Description, Rationale and Evidence
Demographic information	Age, gravidity, parity, estimated gestational age at delivery, weight (kg), height (cm), BMI (kg/m^2) Estimated blood volume on day of surgery (calculated by investigator team): EBV = 65ml x weight (kg) non-obese EBV = 50ml x weight (kg) obese BMI ≥30 Smoking status (yes/no), number of prior cesarean deliveries, race/ethnicity, highest level of education, and household income will be self-reported by subjects. These items relate to social correlates of health that are not otherwise obtainable by surveys. If differences in these characteristics are observed between groups, a regression model will control for these factors (see statistical analysis plan).
Edinburgh Postnatal Depression Scale (EPDS)	The EPDS is self-completed, 10-item scale specifically for women in the perinatal period. It has been shown to be an effective means of identifying patients at risk for depression138,139.
PROMIS Inventories	PROMIS inventories assess core aspects of pain. PROMIS-PI: Pain interference with activities measures external manifestations of pain including social role participation and pain interference (i.e., pain behavior). They are valid and reliable for the constructs that they assess (143-145).
Pain intensity (numeric rating scale)	This question assesses the somatic pain experience. Question: Over the last 24 hours, how intense has your pain been? Please rate on the scale below. 0-10 numeric rating scale where 0 is "no intensity at all" and 10 is "the most intense pain I can imagine"
Pain unpleasantness (numeric rating scale)	This question assesses the emotional pain experience, the emotional valence of pain. Question: Over the last 24 hours, how unpleasant has your pain been? Please rate on the scale below 0-10 numeric rating scale where 0 is "not unpleasant at all" and 10 is "the most unpleasant pain I can imagine"
McGill Pain Questionnaire, Short Form (SF-MPQ)	The McGill Pain Questionnaire Short Form measures multiple dimensions of pain experience including sensory and affective aspects140,141. The instrument is psychometrically sound, valid, reliable, and has good discriminative capacity142. These measures are necessary to better understand the role that these factors play in pain intensity, quality, and duration.
Perceived Stress Scale (PSS)	Psychological stress/distress affects pain, post-operative recovery, and depression. It will be measured in these populations using the validated Perceived Stress Scale.
Daily opioid use	Estimated weekly, daily average (avg) and maximum (max) pill use counts "Over the last week, how many opioid pills have you used every day on average?" "Over the last week, what was the highest number of opioid pills you have needed for pain?"
Opioid use (milligram morphine equivalent, MME)	We will measure oxycodone, hydromorphone and morphine (mg) totals in hospital. These medications will be converted to a single variable, milligram morphine equivalent (MME), per information from the Center for Disease Control

Appendix 2 – Schedule of Perinatal, Surgical, and Infusion-Specific Research Activities

			Study Visit# 1; Day 0—Delivery/Cesarean Surgery -24 hours post-surgery												
Procedures	Prenatal Screening & Baseline Measures	Presurgical Intake T-1 hour *If not completed at baseline*	Cesarean Surgery	Ketamine Infusion 15-45 minutes Post	12-hour Ketamine Infusion								12-hour post-infusion		
					15 Minutes	30 Minutes	Hour 1	Hour 4	Hour 6	Hour 8	10Hour	Hour 12	Hour 16	Hour 20	Hour 24
Informed consent	X														
Demographics and Medical History (inc. Opioid use in hospital)	X	X													
Concomitant medication review	X	X													
Administer study intervention				X											
Maternal Plasma Samples [a]							X		X		X	X			
Adverse event review [b]				X----------X											
Surgical operative survey				X											
Pain Intensity	X	X													
Pain Unpleasantness	X	X													
PROMIS-PI	X	X													
EPDS	X	X													
PSS	X	X													
SF-MPQ	X	X													
RASS [b]					X	X	X	X		X	X	X	X	X	X
Patient Vitals [b]		**X**		X	X	X	X	X	X	X	X	X	X	X	X
LSD Short [b]					X	X	X	X		X	X	X	X	X	X
Side Effect Diary and Patient Acceptability [b]					X	X	X	X		X	X	X	X	X	X

[a] Maternal Plasma Sampling includes analysis of Ketamine, ketamine metabolites (Nor-Ketamine & DKNK), Ketamine R- & S-isomers, cortisol, prolactin, and CYP3A and CYP2B6 enzymes

[b] Adverse Events will result in collection of RASS, LSD short form, Patient vitals, Patient Acceptability ratings, and Maternal plasma sampling at any point between infusion start (t = 0) to 24-hours post-infusion start. LSD score of >8 will trigger a notification to staff and investigator to prompt bedside evaluation.

Appendix 3 – Schedule of Postpartum Research Activities

Procedures All procedures within +/-3 days	Study Visit 2	Study Visit 3	Study Visit 4	Study Visit 5	Study Visit 6	Study Visit 7	Study Visit 8	Study Visit 9	Study Visit 10	Study Visit 11	Study Visit 12	Study Visit 13
	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56	Day 63	Day 70	Day 77	Day 84
Pain Intensity	X	X	X	X	X	X	X	X	X	X	X	X
Pain Unpleasantness	X	X	X	X	X	X	X	X	X	X	X	X
PROMIS-PI	X	X	X	X	X	X	X	X	X	X	X	X
EPDS	X	X	X	X	X	X	X	X	X	X	X	X
PSS	X	X	X	X	X	X	X	X	X	X	X	X
SF-MPQ	X	X	X	X	X	X	X	X	X	X	X	X
Daily opioid use	X	X	X	X	X	X	X	X	X	X	X	X

Appendix 4. Participant Payment per Task

PREPARE 1 Payment						
Patient Tasks	**Timing**	**Payment**		**Patient Tasks**	**Timing**	**Payment**
Baseline Surveys				**Postpartum Surveys**		
Prior to delivery		$60			Week 1	$25
					Week 2	$25
Infusion Payments					Week 3	$25
Plasma Samples (12 ml of blood)					Week 4	$25
Infusion	T 1 hour	$62.50			Week 5	$25
	T 6 hour	$62.50			Week 6	$25
	T 10 hour	$62.50			Week 7	$25
	T 12 hour	$62.50			Week 8	$25
	Total	$250.00			Week 9	$25
					Week 10	$25
Side Effect Diaries					Week 11	$25
Infusion	T 1 hour	$50.00			Week 12	$25
	T 6 hour	$50.00				
	T 10 hour	$50.00			**Total**	$300
	T 12 hour	$50.00				
Post-Infusion	T 16 hour	$50.00				
	T 20 hour	$50.00				
	T 24 hour	$50.00				
	T 12 hour	$50.00			**GRAND TOTAL**	**$1,050**
	Total	$400.00				
Vital Signs						
Infusion	T 1 hour	$5.00				
	T 6 hour	$5.00				
	T 10 hour	$5.00				
	T 12 hour	$5.00				
Post-Infusion	T 16 hour	$5.00				
	T 20 hour	$5.00				
	T 24 hour	$5.00				
	T 12 hour	$5.00				
	Total	$40.00				