STUDY: Perioperative Ketamine in Opioid-Tolerant Patients Undergoing Lumbar Spine Surgery: A Randomized, Double-blind, Place-controlled Trial

Principal Investigator: Jacques E. Chelly, MD, PhD, MBA

IRB: STUDY19020144

NCT: 04220489

Study Protocol – Approved 09/03/2019

Basic Information

1. * **Title of study:**
   Perioperative Ketamine in Opioid-Tolerant Patients Undergoing Lumbar Spine Surgery: A Randomized, double-blind, placebo-controlled trial
2. * **Short title:**
   Perioperative Ketamine in Opioid-Tolerant Patients Undergoing Lumbar Spine Surgery
3. * **Brief description:**
   The goal of this study is to determine whether comprehensive perioperative administration of the NMDA receptor antagonist ketamine can increase postoperative pain tolerance and reduce opiate consumption in chronic back pain patients undergoing spinal laminectomy/fusion when compared to placebo

   Design: Prospective, Randomized, Double-Blind, Placebo Controlled trial involving opiate-dependent patients undergoing lumbar spine surgery. Opioid dependence will be defined as greater than 60 mg oral morphine equivalents/day for greater than one week. Intraoperatively, patients will receive a 1 mg/kg dose of intravenous ketamine or saline with 15 minutes after induction of general anesthesia. Thereafter, a continuous infusion of 0.20 mg/kg/hr ketamine with a maximum dose of 20 mg/hr or saline will be run to conclude at 48 hours after the end of the surgery (fascial closure). The primary outcome measure will be hydromorphone PCA usage during the first 72 hours postoperatively. Secondary outcome measures will be VAS pain scores at rest and with movement in PACU, 24 hr, 48 hr, 72 hr, 2 week (post-op visit), 6 week follow-up visit, as well as, McGill Pain Questionnaire, Pain Catastrophizing Scale, and emotional distress surveys assessing depression and anxiety at preop/screening, postop and 6 week follow-up (PROMIS Emotional Distress-Anxiety Short Form, PROMIS Emotional Distress-Depression Short Form), as well as a Neuro-QOL Short Form v1.1 - Satisfaction with Social Roles and Activities .
4. * **Principal investigator:**
   Jacques Chelly
5. * **Does the investigator have a financial interest related to this research?**
   ○ Yes ◉ **No**
6. * **Will an external IRB act as the IRB of record for this study?**
   ○ Yes ◉ **No**

7. * **What kind of study is this?**
   Single-site study
8. **Attach the protocol:**
   - Sponsor/Multicenter protocol
   - Investigator-initiated protocol
   - Emergency Use Consent/ Protocol/ FDA Form 3926
   - Exempt Application form

	Document	Category	Date Modified	Document History
View	P01 Ketamine Protocol-MG (003).docx(0.01)	IRB Protocol	3/6/2019	History

View: Pitt SF: Funding Sources (not integrated with Grants)

Funding Sources

1. * **Indicate all sources of support:**

   Internal funding

View: Pitt SF: Study Team Members

Study Team Members

1. * **Identify each person involved in the design, conduct, or reporting of the research (includes PI):**

Name	Roles	Affiliation	Involved in Consent	Qualifications
Jacques Chelly	Principal Investigator	Pitt faculty	yes	Jacques E. Chelly, MD, PhD, MBA is a Professor of Anesthesia and Orthopedic Surgery at the University of Pittsburgh Medical Center. He has acted as p... view all

Trent Emerick	Co-investigator	Pitt faculty	yes	Dr. Emerick is a anesthesiologist at Presbyterian Hospital and has participated in research studies
Brian Gierl	Co-investigator	Pitt faculty	yes	Dr. Gierl is an neuro-anesthesiologist at Presbyterian Hospital and has been a co-investigator on prior studies
Michael Gold	Co-investigator	Pitt faculty	no	Michael Gold, PhD is a professor in Neurobiology and Pain Research Center at the University of Pittsburgh. He is extensively knowledgeable in pain re... view all
John Hache	Co-investigator	Pitt faculty	yes	Dr. Hache is an anesthesiologist at Presbyterian Hospital and has been a co-investigator on many research studies
Caroline Kostishack	Secondary Study Coordinator	UPP/UPMC staff	yes	Caroline Stehle (nee Kostishack) is a clinical research coordinator and will be involved in the day to day implementation of the study protocol, incl... view all
Amy Monroe	Primary Study Coordinator	Pitt staff	yes	Ms Monroe is the Manager of the Clinical Trials Program for the Department of Anesthesiology & Perioperative Medicine. She will oversee aspects of th... view all
John Moossy	Co-investigator	Pitt faculty	yes	John Moossy, MD, is a neurosurgeon at UPMC Presbyterian hospital. Participants will be recruited under Dr. Moossy's care.

2. **External team member information: (Address all study team members in item 1. above and leave this section blank)**

Name	Description

There are no items to display

3. **Have you,** Jacques Chelly**, verified that all members of the research team have the appropriate expertise, credentials, training, and if applicable, child**

clearances and/or hospital privileges to perform those research procedures that are their responsibility as outlined in the IRB application?

* (•) **Yes** ( ) No

View: Pitt SF: Study Scope 8.1

Study Scope

Check all that apply

1. * **Will this study actively recruit any of the following populations?**

- [ ] Adults with impaired decision-making capacity
- [ ] Children (under the applicable law of the jurisdiction in which the research will be conducted (<18 years for PA))
- [ ] Children who are Wards of the State
- [ ] Employees of the University of Pittsburgh/UPMC
- [ ] Medical Students of University of Pittsburgh as primary research group
- [ ] Students of the University of Pittsburgh
- [ ] Neonates of uncertain viability
- [ ] Non-viable neonates
- [ ] Non-English speakers
- [ ] Nursing home patients in the state of Pennsylvania
- [ ] Pregnant women
- [ ] Prisoners
- [x] **N/A**

2. * **Will any Waivers be requested?**

- [ ] Waiver/Alteration of Consent
- [ ] Waiver to Document Consent
- [ ] Waiver/Alteration of HIPAA
- [ ] Exception from consent for emergency research
- [x] **N/A**

3. * **Will this study involve any of the following?**

- ☐ Specimens
- ☐ Honest Broker to provide data/specimens
- ☐ Return of Results to Subjects or Others
- ☐ Fetal tissue
- ☑ **N/A**

4. * **Will Protected Health Information be collected?**

- ☐ Pitt medical records
- ☑ **UPMC medical records**
- ☐ Other Institutions' medical records
- ☐ N/A

5. * **Other Requests?**

- ☐ Deception (if not Exempt, also requires Waiver/Alteration of Consent)
- ☐ Emergency Use / Single Patient Expanded Access
- ☑ **Placebo Arm**
- ☐ Withdraw from usual care
- ☐ N/A

6. * **Determining Scientific Review:**
Department Scientific Review (DOD requires departmental review)

* **Choose the appropriate organization to conduct the scientific review:**
U of Pgh | School of Medicine | Anesthesiology

7. * **Has this study (or substantially similar study) been previously disapproved by the Pitt IRB or, to your knowledge, by any other IRB?**

○ Yes ◉ **No**

Review the HRPO policy, if participating in research at the VA Pittsburgh Healthcare System or using funding from the VA

8. * **Does the study use an approved drug or biologic, use an unapproved drug or biologic, or use a food or dietary supplement to diagnose, cure, treat, or mitigate a disease or condition?**

◉ **Yes** ○ No

9. * **Does the study evaluate the safety or effectiveness of a device?**

○ Yes ◉ **No**

10. * **Is this application being submitted to convert an approved study from OSIRIS to PittPRO?** (Tip Sheet)

○ Yes ◉ **No**

View: Pitt SF: Drugs

Drugs

1. * **List all drugs, biologics, foods, and dietary supplements to be used in the study:**

	Generic Name	Brand Name	Attachment Name
View	Ketamine	Ketalar	Ketamine package insert.pdf FDA exempt.pdf memo signed.pdf

2. * **Will the study be conducted under an investigational new drug application (IND) or radiation human subcommittee (HUSC)?**

○ Yes ◉ **No**

3. **Attach files:** (such as IND, HUSC, or other information that was not attached for a specific drug)

Document	Category	Date Modified	Document History

There are no items to display

4. * **Describe your plan to store, handle, and administer drugs so that they will be used only on subjects and be used only by authorized investigators:**
The study drug and saline placebo will be sourced by the Department of Pharmacy's Investigational Drug Service (IDS) at UPMC Presbyterian Hospital. The drug will be stored, handled and dispensed in accordance with Department of Pharmacy IDS guidelines to ensure the correct patient receives the drug and will only be administered under an investigator's order. .

5. * **Do you plan to utilize the UPMC Investigational Drug Service (IDS) to dispense the drug?**

   (•) **Yes** ( ) No

View: Pitt SF: Local Site Documents

Click **Continue** as this page was intentionally left blank.

View: Pitt SF: Research Sites

Research Sites

1. **Choose all sites that apply:**

   UPMC

2. * **Select the UPMC sites where research will be conducted:**

   Presbyterian
   Other UPMC Site- Specify below:

3. **List the Other UPMC sites:**
   UPMC Neurosurgery Clinic

4. **Describe the availability of resources and the adequacy of the facilities to conduct this study:**
   The PI has adequate time to dedicate to the completion of this project, and adequate staffing and support through the clinical research coordinators assigned to this project. Protected servers are available through UPMC and will be used for the creation and storage of protected health data collected in the course of this research. The PI has access to and will be supervising an electronic password-protected database.

   There is adequate and appropriate space for these research activities at Presbyterian Hospital where this research will be conducted. All research interventions/activities will be conducted in private patient care areas. This facility is adequate for the performance of all study procedures, and for handling emergency situations should they arise.

   Prospective subjects will be approached for consent in the UPMC Neurosurgery Clinic while doing their preoperative evaluations by a study coordinator and /or acute pain service member.

Study Aims

1. * **Describe the purpose, specific aims, or objectives and state the hypotheses to be tested:**
   The goal of this study is to determine whether comprehensive perioperative administration of the NMDA receptor antagonist ketamine can reduce postoperative pain tolerance and opiate consumption in chronic back pain patients undergoing spinal laminectomy/fusion when compared to saline placebo.

   Investigators hypothesize that administration of a ketamine infusion intraoperatively and for 48 hours postoperatively will significantly reduce postoperative opiate consumption and VAS pain scores in chronic back pain patients undergoing spinal laminectomy/fusion when compared to those in the placebo arm.

2. * **Describe the relevant prior experience and gaps in current knowledge including preliminary data. Provide for the scientific or scholarly background for, rationale for, and significance of the research based on existing literature and how it will add to existing knowledge:**
   Patients with chronic pain are some of the most difficult to manage during the perioperative period, in part because they are often on large doses of opioids, rendering them relatively tolerant to the opioids used in the perioperative period. Several lines of evidence suggest that ketamine, administered intraoperatively, and/or post-operatively may be solution to this problem. Even more intriguingly, there is evidence to suggest that perioperative ketamine may have long term effects on opioid use. However, nearly all of the studies up to this point have investigated the short-term effects of ketamine on post-operative pain and opioid consumption. This pilot study will investigate the impact of intra-operative and post-operative ketamine on pain and opioid consumption six weeks after surgery and will support a larger NIH funded trial.

   Central Sensitization and the NMDA receptor: evidence from preclinical models of pain

   Seminal studies by Woolf and colleagues provided mechanistic insight into a phenomenon long appreciated by patients and clinicians alike: intense noxious stimulation results in an increase in pain from the site injury as well as from surrounding tissue well outside the injured tissue. The

amplification and spread of the pain arising from the injured tissue is due, in at least in part to changes in the central nervous system in a process called central sensitization. Of particular relevance to the present proposal, the sensitization is critically dependent on spinal glutamatergic receptors, and in particular, the N-methyl-D-aspartate (NMDA) receptor (Wilcox, 1991; Davies, 1987; Dickenson, 1987) The NMDA receptor is a ligand gated ion channel which is activated by the endogenous agonist glutamate. The channel is subject to voltage-dependent block by endogenous Mg2+. Ketamine is a non-competitive antagonist of the NMDA receptor, binding to a site near the pore region that bind other antagonists such as MK-801 and memantine (Paolettia,2007). Blockade of the NMDA receptor by ketamine (Laird,1995) and other NMDA receptor antagonists (Fisher,2000) has been shown to inhibit development of hyperalgesia in several preclinical animal models of chronic pain.

Opioid receptor agonists such as morphine are still the most efficacious medications available for the treatment of moderate to severe pain. One of the major limitations to the long term use of these compounds, however, is the development of tolerance. While the mechanistic details linking opioid and NMDA receptors have yet to be fully elucidated, there is compelling preclinical evidence that the development of tolerance depends on NMDA receptor activation: the development of tolerance is blocked by the administration of the non-competitive NMDA receptor blocker, MK-801 (Marek, et al 1991). This potential role of the NMDA receptor in both mechanisms of tolerance formation and hyperalgesic states make it an attractive target for opioid-dependent patients undergoing surgical procedures.

Clinical Studies of Ketamine in post-operative pain

The analgesic and/or opioid sparing effects of ketamine has been studied in healthy subjects and pain patients including those suffering from glossopharyngeal neuralgia, postherpetic neuralgia, fibromyalgia muscle pain, stump and phantom limb pain, peripheral neuropathic pain, central neuropathic pain, chronic post-traumatic pain, pain due to arteriosclerosis obliterans (Fisher, 2000). The application of ketamine to the perioperative period as a "preemptive" or "preventive" analgesic has met with mixed results. Many of the earlier studies compared a preincisional with a postincisional dose of ketamine and saw no difference between the two. However a meta-analysis of 37 subsequent trials of the use of perioperative ketamine compared to placebo found that "ketamine in subanaesthetic dose is effective in reducing morphine requirements in the first 24 hours after surgery and also reduces postoperative nausea and vomiting" and "adverse effects are mild or absent." (Bell, 2006). Twenty-seven of 37 trials found that perioperative ketamine reduced rescue analgesic requirements or pain intensity, or both. Ten trials found no significant difference between ketamine and placebo, three of which were considered non-sensitive. Of

those that did find an effect, it was generally reported to give a 30-50% reduction of rescue analgesics. Another review that used VAS scores at 24 hours after surgery as the primary outcome, and included an overlapping subset of studies did not find an overall significant effect of ketamine (Subramaniam, 2001).

Dose Range and side effects

There is an important difference in the dose range for ketamine's anesthestic and analgesic effects. In the Cochrane review, the majority of studies investigated the effect of bolus dosing, although some included ketamine as part of a PCA. The doses used in these studies ranged from 10-270 mg, all of which are considered to be subanesthetic in that they elicited rare or no side effects. There did not appear to be a benefit to increasing the total dose above 30 mg/24 hr (Bell, 2006).
In more recent studies, Tucker et al found a clinical benefit through the co-administration of ketamine with fentanyl at measured serum concentrations of 30–120 ng/ml, while side effects (visual hallucination, sedation) occurred at serum concentrations in excess of 200 ng/ml (Tucker, 2008). Yamauchi et al found that a ketamine infusion of 2 mg/kg/day (approx. 5.4 mg/hr in 70 kg patient) yielded a serum concentration of 50 ng/ml, and enhanced fentanyl PCA-induced postoperative analgesia (Yamauchi, 2005). Side effects that were observed in some of the previous studies were relatively rare and included some increased sedation, dysphoria, typically within the first 1-2 hours after a bolus dose 13.

Application of ketamine to specific patient populations
Most of the studies listed in the Cochrane and other reviews enrolled patients with no previous chronic pain syndrome. However, patients with chronic pain are some of the most difficult to manage during the perioperative period, in part because they are often on large doses of opioids prior to surgery. As a result, they are relatively tolerant to the doses of opioids used in the perioperative period. In one sense, chronic pain patients have already proven themselves to be sensitive to NMDA receptor activation, in that they already exhibit hyperalgesia, and a degree of opioid tolerance, both of which are NMDA receptor-dependent processes. The anecdotal experience of UPMC's acute pain service is that many of the chronic pain patients respond well to a low dose of ketamine infusion in the postoperative period. One very recent study specifically investigated chronic back pain patients, and found that an intraoperative bolus and intraoperative infusion of ketamine resulted in lower total analgesic consumption and lower pain scores during post the immediate post-op period as well as 6 weeks after surgery (Loftus, 2010), suggesting that ketamine may also have long-term benefits in chronic pain patients undergoing surgery.

Nearly all the studies up to this point have investigated a single administration or a brief intraoperative infusion of ketamine, and thus ketamine is likely eliminated from the system shortly after the conclusion of the surgery, potentially limiting the full efficacy of this therapy. NMDA receptors are likely to still be active in the post-operative period (i.e. end of surgery- 48 hours post-surgery), because of the continued activation of nociceptors as a result of processes activated by tissue damage. This is also the timeframe when tolerance to opioids is most problematic because it is when patients experience the most pain. Therefore, we predict that the use of ketamine during the post-operative period will not only enable better pain management over this time frame, but will have an even more significant long term impact on pain and opioid use.

View: Pitt SF: Recruitment Methods

Recruitment Methods

* **Will you be recruiting individuals for participation in this study?**

(•) **Yes** ( ) No

1. * **Describe who will be recruiting individuals for participation for this study:**
   The Principal Investigator, Neurosurgeon Co-Investigators, and study coordinator

2. * **Select all methods to be used for recruitment:**

- [x] **Directly approaching potential subjects (in-person)**
- [ ] Email/Listserv/Electronic Mailing List
- [ ] Flyers/Posters or Brochures
- [ ] Letters sent to potential participants
- [ ] Newspaper/Magazine advertisements
- [ ] Pitt+Me
- [ ] Radio/Television/Video announcements
- [ ] Telephone scripts
- [ ] Website/Social Media
- [ ] Registries

☑ **Other**

3.

* **Enter description of 'Other' method of recruiting:**
medical record review
Neurosurgery Clinic Schedule

4. * **Provide details on your recruitment methods:**
Patients will be recruited from the UPMC Neurosurgery Clinic. The patient's medical record will be reviewed to assess for inclusion criteria including confirming that the patient is undergoing lumbar spine surgery of at least one level and no more than 4 levels, that the patient has chronic back pain (>3 months), is considered ASA 1-3, is of the age 18-65 and is opiate-dependent, meeting both of the following criteria:
a. Daily opiate use for at least 2 months
b. Oral morphine equivalent of 60 mg/day or higher
This medical record review to identify eligible candidates is minimal risk and that the rights and welfare of subjects will not be adversely affected
The primary surgeon will identify patients who are prescreened via medical record to be eligible for inclusion, ask them if they would be interested in participating, and if so, the enrollment and consent process would be initiated. Participating neurosurgeons include Drs. Moossy, who will identify eligible patients. Informed consent will be performed by this Neurosurgeon, the PI, or other co-investigator in the study. Enrollment will be performed by the study coordinator and/or trained representative from the Acute Interventional Perioperative Pain Service (AIPPS). Enrollment will include review of eligibility, and detailed explanation of the study.

5. * **Describe all compensation/incentives offered to participants and timing of these offers:**
Participants will be compensated up to $100 for travel and parking expenses related to Pre-Op Visit ($50) and 6-Week Follow-up visit ($50)

6. **Recruitment materials:** (attach all material to be seen or heard by subjects, including advertisements and scripts)

Document	Category	Date Modified	Document History
There are no items to display			

View: Pitt SF: Study Design

Study Design

1. **Total number of subjects to be enrolled at this site (enter -1 for chart reviews, banking, registries):**
   20

2. **Describe and explain the study design:**
   This study is being proposed as a pilot study to inform the feasibility and direction of a larger P01 NIH funded trial.

3. **Describe the primary and secondary study endpoints:**
   Primary Outcome measure:
   ¬ Pre- and post-surgical pain rating
   ¬ Pre- and post-surgical opioid utilization (in morphine equivalent units in the PACU and post-operative period until discharge, at 14 days, and at 6 weeks follow-up)
   ¬ Pre- and post-surgical opioid analgesic efficacy

   Secondary outcome measures:
   ¬ Mcgill Pain Questionnaire-Short Form
   ¬ Pain Catastrophizing Scale
   ¬ PROMIS Emotional Distress-Anxiety Short Form
   ¬ PROMIS Emotional Distress-Depression Short Form
   ¬ Neuro-QoL Short Form v1.1 - Satisfaction with Social Roles and Activities
   ¬ Cold Pressor Test

   .

4. **Provide a description of the following study timelines:**

   Duration of an individual subject's active participation:
   6 weeks
   Duration anticipated to enroll all subjects:
   5 months
   Estimated date for the investigator to complete this study (complete primary analyses):
   10/31/2019

5. **List the inclusion criteria:**
   Patients undergoing lumbar spine surgery of at least one level, and no more than 4 levels.
   Patients with chronic back pain (>3 months)
   ASA 1-3
   Age 18-65
   Opiate-dependent, meeting both of the following criteria:
   1.Daily opiate use for at least 2 months
   2. Oral morphine equivalent of 60 mg/day or higher

6. **List the exclusion criteria:**
-Intolerance or known allergy to ketamine
-History of increased intraocular pressure (> 22mmHg)
-Uncontrolled hypertension (systolic blood pressure greater than or equal to 180, diastolic blood pressure greater than equal to 100)
-Increased intracranial pressure (signs including:Behavior changes, -Decreased consciousness, Headache, Lethargy
-Neurological symptoms, including weakness, numbness, eye movement problems, and double vision, seizures, vomiting)
History of psychosis
Pregnancy
Patients with significant liver disease (signs and symptoms of liver injury, such as discolored skin and eyes that appear yellowish, abdominal pain and swelling, Itchy skin that doesn't seem to go away, Dark urine color, Pale stool color, Bloody or tar-colored stool, Chronic fatigue, Nausea, Loss of appetite, with or without elevated LFTs: AST > 120 IU/ml, AP >130 IU/ml, and ALT >40 IU/ml)
-Patients with exposure to CYP3A and / or CYP2B6 inhibitors, including the herbs and the over-the-counter compounds (list of drugs can be found at http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm)

7. **Will children or any gender, racial or ethnic subgroups be explicitly excluded from participation?**

(•) **Yes** ( ) No

* **Identify the subgroups and provide a justification:**
Presbyterian Hospital is an adult-only facility

8. **Describe the power analysis used and cite your method of statistical analysis. If a power analysis is not possible, thoroughly justify the sample size required for the study, including appropriate literature citation (alternatively provide page reference in attached protocol):**
This is a pilot to support a P01 program pilot application to the NIH, so the data will be analyzed mainly using descriptive statistics. Additional statistical analysis methods such as a 2-sample t test to compare significance between groups may also occur.

View: Pitt SF: Research Activities

Research Activities

1. * **Provide a detailed description of all research activities (including screening and follow-up procedures) that will be performed for the purpose of this research study. This description of activities should be complete and of sufficient detail to permit an assessment of associated risks.**
Patients will be recruited from the UPMC Neurosurgery Clinic. The primary surgeon will identify patients who would be eligible for inclusion, ask them if they would be interested in participating, and if so, the enrollment and consent process would be initiated. The participating neurosurgeon is Dr. Moossy, who has agreed to allow us access to his patients. Informed consent will be performed by Dr. Moossy, or the PI. Enrollment will be performed by the study coordinator and/or trained representative from the Acute Interventional Perioperative Pain Service (AIPPS). Enrollment will include review of eligibility, and detailed explanation of the study.

Screening Visit: Approximately 1 hour
After patients are enrolled into the study at the preoperative neurosurgery clinic, a number of forms will filled out by the subjects: McGill Pain questionaire-Short form (measures pain), pain medication review form, and the Pain Catastrophizing Scale (PCS) (assesses patient's ability to tolerate pain) PROMIS Emotional Distress-Anxiety Short Form (measures anxiety) and PROMIS Emotional Distress-Depression Short Form (measures depression), Brief Psychiatric Rating Scale (assesses psychiatric state of patient) and Neuro-QoL Short Form v1.1 - Satisfaction with Social Roles and Activities (assesses depression/anxiety when it comes to social roles) will also be completed.

Pre-Operative Visit: Approximately 1.5 hrs

The subject will be asked to come into the Aiken Medical Building, Suite 407 on a date after the clinic visit but before their day of surgery for a Pre-Operative Visit. Investigators will work with the subject to determine their opioid dose regimen, and the subject will be asked to come into the Aiken Medical Building thirty minutes before their opioid dose is due and will be asked to bring with them their upcoming dose of pain medication. Prior to taking their pain medication, the subject will then be administered a cold-pressor pain sensitivity test. For this test, the subject will place their non-dominant hand in a bowl of ice water up to the wrist. Pain threshold is defined as the time in seconds that is takes for the subject to first report the sensation of pain in the immersed hand. Pain tolerance is defined as the time in seconds that it takes for the subject to withdraw their hand from the ice water because it has become too uncomfortable for them to keep their hand immersed any longer. A cut-off of four minutes will be imposed to limit the potential for any tissue damage. At this time, the subject will be asked to remove their hand from the ice water, even if they say that they could keep their hand immersed for longer. Pain threshold, tolerance and cut-off will be recorded using a stop watch. Heart rate and blood pressure

will be recorded before and after the cold-pressor test. Once the cold pressor test is completed, the McGill Pain Questionnaire will be administered. After this questionnaire is complete, the subject will take the dose of opioid medication they have brought from home and are scheduled to receive and will wait in the clinic for 30 minutes for the pain medication to take effect. Once the 30 minutes is complete, the cold-pressor test will be repeated, heart rate and blood pressure collected before and after, and McGill Pain Questionnaire will be administered again. Opioid-analgesic efficacy will be estimated by the change in pain threshold and tolerance observed after the opioid was consumed relative to initial assessment of pain threshold and tolerance. The subject will be compensated $50 for this pre-operative visit.

Surgical Visit:

Study groups:
Patients will be randomized to one of the following groups:
1. Intraoperative ketamine- post operative 48 hr ketamine infusion
2. Intraoperative placebo (saline)- post operative placebo (saline) infusion

Randomization will occur by a computer based system at a 1:1 ratio. The Investigational Drug Pharmacy will create the randomization log and IDS will randomize the subject independent of the research team. The study drug/placebo will look identical to maintain the blind for all clinicians and research staff involved.

At the day of surgery, subjects will be seen by team members of the Acute Interventional Perioperative Pain Service preoperatively. Pregnancy will be assessed via medical record, as it is standard of care for these patients to take a pregnancy test day of surgery. Since the ketamine infusion will occur for 48 hours while patient is in the hospital, there is little risk of becoming pregnant during study drug treatment period

Enrolled participants will receive a 1 mg/kg dose of intravenous ketamine or saline 15 minutes after induction of general anesthesia. Thereafter, a continuous infusion of 0.20 mg/kg/hr ketamine or saline with a maximum dose of 20 mg/hr will be run to conclude at 48 hours after the end of the surgery (fascial closure).

A standardized general anesthesia protocol will be used by the hands-on provider. All drugs used intraoperatively, including total hydromorphone dose, will be collected from the electronic medical record. .

The amount of narcotics and non-narcotic analgesics administered in the operative and postoperative period will be collected from the electronic chart from day of surgery until discharge. VAS pain scores will be collected

from the PACU until discharge from the hospital.

Pain will be monitored every four hours, except during the night when the participant is asleep. We will use a scale from 0-10, 0 being no pain, 5 being moderate pain and 10 being the worst imaginable pain. The participant will also be asked to score pain at its best and worst over the period since they were last asked.

Post-Op Visit: Approximately 1 hour

Patients will follow-up at Neurosurgery clinic at 10-14 days postoperatively. At this time daily opioid usage will be assessed and converted to morphine equivalents/24 hr. At this visit, the McGill Pain questionnaire-Short form, pain medication review form, and the Pain Catastrophizing Scale (PCS) (Sullivan, 1995). PROMIS Emotional Distress-Anxiety Short Form and PROMIS Emotional Distress-Depression Short Form, Brief Psychiatric Rating Scale and Neuro-QoL Short Form v1.1 - Satisfaction with Social Roles and Activities will also be completed by the participant.

6-Week Follow-Up Visit: Approximately 1.5 hours

The subject will be asked to come to the Aiken Medical Building, Suite 407 approximately 6 weeks after their surgery for a 6-Week Follow-Up Visit. Investigators will work with the subject to determine their post-operative opioid dose regimen, and the subject will be asked to come in for the visit thirty minutes before their opioid dose is due and bring with them their upcoming dose of pain medication. Prior to taking their pain medication, the subject will then be administered a cold-pressor pain sensitivity test, in a manner identical to that use during the pre-operative assessment.In addition to the McGill Pain Questionnaire-Short form, a pain medication review form, the Pain Catastrophizing Scale (PCS) (Sullivan, 1995), the PROMIS Emotional Distress-Anxiety Short Form, the PROMIS Emotional Distress-Depression Short Form, Brief Psychiatric Rating Scale and Neuro-QoL Short Form v1.1 - Satisfaction with Social Roles and Activities will also be completed. The subject will be compensated $50 for this 6-week follow-up visit.

2. **Upload a copy of all materials used to collect data about subjects: (Attach all surveys, interview/focus group scripts, and data collection forms except for case report forms, SCID or KSADS):**

	Document	Category	Date Modified	Document History
View	Brief Psychiatric Rating Scale (0.01)	Data Collection	3/6/2019	History
View	PROMIS v1.0 ED-Depression Short Form 1.pdf(0.01)	Data Collection	3/6/2019	History
View	PROMIS v1.0 ED-Anxiety Short Form 1.pdf(0.01)	Data Collection	3/6/2019	History
View	Pain%20catastrophizing%20scale-1.docx(0.01)	Data Collection	3/6/2019	History
View	Neuro-QOLv1.1-SatisfactionwithSocialRolesandActivitiesSF_03-06-2014.pdf(0.01)	Data Collection	3/6/2019	History
View	Medications- questionaire.doc(0.01)	Data Collection	3/6/2019	History
View	Mcgill pain questionaire.docx(0.01)	Data Collection	3/6/2019	History

3. * **Will blood samples be obtained for research purposes?**

○ Yes ◉ **No**

View: Pitt SF: Consent Process

Consent Process

Enter N/A in response to the following questions if a Waiver of Consent is requested for all research activities or if no subjects are being enrolled.

1. * **Indicate where the consent process will take place and at what point consent will be obtained:**

Patients will be recruited from the UPMC Neurosurgery Clinic. The primary surgeon will identify patients who would be eligible for inclusion, ask them if they would be interested in participating, and if so, the enrollment and consent process would be initiated. Participating neurosurgeons include Drs. Moossy, who will identify eligible patients. Informed consent will be performed by this Neurosurgeon, the PI, or other co-investigator in the study. Enrollment will be performed by the study coordinator and/or trained representative from the Acute Interventional Perioperative Pain Service

(AIPPS). Enrollment will include review of eligibility, and detailed explanation of the study.

2. * **Describe the steps that will be taken to minimize coercion and undue influence, including assurance that there is sufficient time for subjects to make an informed decision:**
In order to minimize the possiblity of coercion or undue influence, the patients will be first informed that the choice of particpation in the study is totally voluntarily in nature, and they will receive a standard of care when they decide not to participate in the study. Prospective patients will be encouraged to ask questions and to discuss the study with others during the consent process. Then, they will be assured that after participation in the study, they will receive either ketamine or placebo in a randomized fashion if they participate in the study. Informed consent will occur in the neurosurgery clinic during their pre-surgical clinic visit.

3. **For studies that involve multiple visits, describe the process to ensure ongoing consent:**
At each visit, the subjects will be asked if they have any questions and will be reminded about the goals and objectives of the study. The subjects will also be reminded that they can withdraw from the study at any time.

4. * **Steps to be taken to ensure the subjects' understanding:**
Individuals will be provided with full explanation of study-related goals and procedures. Questions will be answered from the patient as well as their family members as necessary. Patients will be given as much time as necessary to read the consent form and ask questions.

5. * **Are you requesting an exception to the IRB policy related to the informed consent process:**
○ Yes ◉ **No**

View: Pitt SF: Consent Forms

Consent Forms

1. **Consent Forms:**

	Document	Category	Date Modified	Document History
View	Consent draft_Version 4.3.19.docx(0.03)	Consent Form	4/3/2019	History

2.

Refer to the following templates and instructional documents:

- Guidance - Consent Wording
- Template - Consent Document - Short Form
- HRP-090 - SOP - Informed Consent Process for Research
- HRP-091 - SOP - Written Documentation of Consent

View: Pitt SF: Medical Records

Medical Records

1. **You are required to submit this study to the Research Informatics Office, Health Record Research Request (R3). Per UPMC Policy HS-RS0005, all research projects that access or involve UPMC electronic protected health information (e-PHI) must be submitted to R3, with the exception of clinical trials that are contracted through the UPMC Office of Sponsored Programs and Research Support (OSPARS).**

Complete the R3 intake form available at http://rio.pitt.edu/services. An R3 representative will conduct a review. You will be notified once your R3 review is complete or if anything further is needed.

*** Describe the protected health information that will be collected from the covered entity and/or the research derived information that will be placed into the medical records:**
Patient demographics and medical history will be collected from the medical record

The amount of narcotics and non-narcotic analgesics administered in the operative and postoperative period will be collected from the electronic chart from day of surgery until discharge. VAS pain scores will be collected from the PACU until discharge from the hospital.

View: Pitt SF: Electronic Data Management

Electronic Data Management

1. *** Will only anonymous data be collected (**select **NO** if identifiers will be recorded **at anytime during the conduct of the study)?**

○ Yes ◉ **No**

Select all identifiers to be collected during any phase of the research including screening:

Name:	☑	**Internet Protocol (IP) Address:**	☐
E-mail address:	☐	**Web Universal Resource Locators (URLs):**	☐
Social security #:	☐	**Social security # (for Vincent payment only):**	☑
Phone/Fax #:	☑	**Full face photo images or comparable images:**	☐
Account #:	☐	**Health plan beneficiary #:**	☐
Medical record #:	☑	**Device identifiers/serial numbers:**	☐
Certificate/license #:	☐	**Vehicle identifiers/serial #/license plate #:**	☐
		Biometric identifiers, finger and voice prints:	☐

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* **a: Will you be collecting any of the following location data: geographic subdivisions smaller than a State such as street address, city, county, precinct, zip, geocodes, etc.?** ◉ Yes ○ No

* **b: Will you be collecting any date information such as birth date, death, admission, discharge, date of surgery/service?** ◉ Yes ○ No

c: List any other unique identifying numbers, characteristics or codes related to an individual that are to be collected:

* **d: Provide a justification for recording Social Security numbers including why it's required, where it's stored, how it's protected and who will have access:**

Will be collecting SSN's only for Vincent payment, only the PI and coordinator will have access to the SSN's and only for the purpose of setting up Vincent payments. SSN's will be collected separately from the study data and destroyed after Vincent payment has been set up.

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* **For ALL identifiable data collected, will you be coding the data by removing the identifiers and assigning a unique study ID/code to protect the identity of the participant?** (●) **Yes** ( ) **No**

* **Will the data be HIPAA de-identified?** (●) **Yes** ( ) **No**

* **Briefly describe your plan to store coded data separately from the identifiable data:**

To protect against the possibility of breach of confidentiality, all data collected will be identifiable only by an unique subject ID number, and no personal identifiers will be stored with the data. Linkage files identifying subjects will be stored only in the UPMC server and will be linked to the physical record with a subject code. Physical records will be kept in locked files accessible only by study staff; electronic data will be handled and protected as described above on the UPMC server.

2. * **Will sensitive data be collected (e.g., protected health information, mental health, medications, drug/alcohol use, illegal behaviors)?**

(●) **Yes** ( ) No

3. * **Select all locations where data will be stored or accessed (including e.g., personal / employer laptop or desktop):**

	Storage Device	Description	Identifiable Data	Sensitive Data	De-Identified/Anonymous Data
View	UPMC owned desktop, laptop or other device		no	no	no
View	Server: UPMC Managed Server		yes	yes	yes

4. * **Select all technologies being used to collect data or interact with subjects:**

N/A

View: Pitt SF: Data Safety and Monitoring

Data Safety and Monitoring

1. * **Describe your plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe. The plan might include establishing a data monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor:**
   The proposed study will use the FDA definition of adverse events (AE) and serious adverse events (SAE). Any SAE, which is unexpected and related to study intervention, will be reported immediately to the IRB and will be followed by an additional letter detailing the nature of the SAE. In the event that a participant either withdraws from the study or the investigators decide to discontinue a participant due to a SAE, the participant will be monitored by the co-PIs until (a) a resolution is reached (e.g., the problem has resolved or stabilized with no further change expected), (b) the SAE is determined to be clearly unrelated to the study intervention, or (c) the SAE results in death. Outcomes of SAEs will be regularly reported to the IRB and the sponsor. A summary of the SAEs that occurred during the previous year will be included in the annual progress report as well as in the annual IRB renewal.
   If an unexpected adverse event occurs, the investigators will re-assess the risk-benefit ratio of the study and submit any modifications deemed necessary to the IRB for approval. If necessary, protocol refinement will occur to address safety concerns and/or adjustments necessary based on laboratory refinement, practitioner and/or patient acceptability, or other issues that may be uncovered.

   Data will be continuously monitored by study coordinator and PI when subjects are being actively treated and are in the hospital. The PI and study coordinator will review questionnaire and cold-pressor data weekly.
2. * **Describe your plan for sharing data and/or specimens:**
   In the future, the investigators may decide to share data with other investigators both within and outside of this institution. If that were to occur, we would de-identify all of the information prior to sharing any data in this way.
3. **If any research data is collected, stored, or shared in a paper format, address what precautions will be used to maintain the confidentiality of the data:**
   Paper-based records will be kept in a secure location, computer-based files will be available to personnel involved in the study through access

privilege, whenever possible identifiers will be removed from study-related information, patients' computer medical information will only be available through password access.

Identifiable data will be kept in a single encrypted file on the shared (z:) drive behind the UPMC firewall. All other study-related data (such as paper records and data for analysis) will have all identifiers removed.

View: Pitt SF: Risk and Benefits

Risk and Benefits

1. * **Enter all reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related to subjects' participation in the research:**

View

Research Activity	**Collection of information from medical records**
Common Risks	***No Value Entered***
Infrequent Risks	**Breach of confidentiality**
Other Risks	***No Value Entered***

View

Research Activity	**completion of questionnaires**
Common Risks	***No Value Entered***
Infrequent Risks	**feelings of frustration, embarrassment or boredom**
Other Risks	***No Value Entered***

View

Research Activity	**low dose ketamine infusion**
Common Risks	***No Value Entered***
Infrequent Risks	**Allergic Reaction (rare) Blurred vision(infrequent) Confusion (infrequent) Drowsiness (infrequent) Increased or decreased blood pressure or heart rate (infrequent) Mental or mood changes (infrequent) Nausea and vomiting (infrequent) Dreams, hallucinations and delirium (infrequent) Liver injury (rare)**
Other Risks	**With respect to the risk of liver injury, there have been reports of reversible, elevated liver enzymes associated with long term, repetitive use of high dose ketamine, although there are currently no reports of liver injury associate with low dose ketamine, which is used in this study. That being said, you are instructed to notice the following signs and symptoms of liver injury, and**

	report to physicians with the information of previous exposure of ketamine infusion: • Discolored skin and eyes that appear yellowish • Abdominal pain and swelling • Itchy skin that doesn't seem to go away • Dark urine color • Pale stool color • Bloody or tar-colored stool • Chronic fatigue • Nausea • Loss of appetite

View

Research Activity	cold pressor test
Common Risks	*No Value Entered*
Infrequent Risks	Excessive painful sensation (rare) tissue damage (rare)
Other Risks	*No Value Entered*

2. * Describe the steps that will be taken to prevent or to minimize risks:

Experimental Interventions:

Participants will receive ketamine infusion at the in-patient units. Should any complications associated with the medication occur, emergency cart is readily available at the units. Acute Interventional Perioperative Pain Service (AIPPS), which is responsible for the participants' postoperative pain management, is 24/7 available to address any associated issues.

All aspects of patients' analgesic care, including the management of low-dose ketamine infusion, will be administered under the consultation of the acute Interventional Perioperative Pain Service, which routinely uses these infusions in the managment of perioperative pain in opioid dependent or difficult to treat patients. This service is on call 24 hours/day. Ketamine infusions will only be administered to inpatients who are on floors where nursing staff has undergone training in the managment and administration of low dose ketamine infusions.

Patients will be instructed to notice the signs and symptoms of liver injury and report to medical staff about previous exposure to ketamine infusion. Patients will also be followed up for mental status change with Brief Psychiatric Rating Scale.

If the subject is particularly sensitive to the cold pressor test, they will be encouraged to move hand from the ice as soon as they feel any pain sensation. There is a four-minute limit on the test to reduce any risk of tissue damage. The participant will be made aware that they can refuse the cold pressor test should they choose.

Investigators who will access the identifiable medical records already have normal clinical access to all necessary records, as granted by the privacy office for job-related needs. Thus, only HIPAA trained research staff will be handling this information and this information will be stored in a locked

database protected by the UPMC firewall. Additionally, all data generated under this protocol will be monitored and maintained by the principal investigator. Any databases that contain identifiable information will be stored on a departmental drive on the UPMC network created for the principal investigator, and all data will be deidentified according to the HIPPA "safe harbor" guidelines prior to statistical analysis.

Pregnancy is being assessed via a medical record review. Since the ketamine infusion will occur for 48 hours while patient is in the hospital, there is little risk of becoming pregnant during study drug treatment period.

The follow up contact will be made by trained physicians.

3. **Financial risks - will the subject or insurer be charged for any research required procedures?**

   ○ Yes ◉ **No**

4. **Describe the steps that will be taken to protect subjects' privacy:**
   Research intervention will be conducted in a private room with the patient, collected information will be limited to that which is necessary for the goals of the research study, access to the patient's private information will be limited to those involved in the patient's medical care.

5. **What steps will be taken in the event that a clinically significant, unexpected disease or condition is identified during the conduct of the study:**
   The patient's primary medical team will be immediately notified of the unexpected, clinically significant condition. The patient's clinically significant medical condition will be managed accordingly. If any of the clinically significant medical condition is related to the study, then the patient's participation in the study will be re-evaluated, with the possibility of the patient being withdrawn from the study if this leads to the resolution of the clinically significant medical condition

6. **Describe the potential benefit that individual subjects may experience from taking part in the research or indicate if there is no direct benefit. Do not include benefits to society or others:**
   Patients with chronic pain and opioid dependence may experience better analgesia in the postoperative period. There is no guaranteed direct benefit to participants.

7. **Do you anticipate any circumstances under which subjects might be withdrawn from the research without their consent?**

   ◉ **Yes** ○ No

* **Describe the circumstances and any procedures for orderly termination:**
Subject's failure to follow study procedures
Severe allergic reaction to study drug

8. **Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection and data already collected:**
If a participant withdraws from research, follow up will cease but data previously collected may still be used in analysis.

View: Pitt SF: Placebo Arm

Placebo Arm

1. * **Is there a commonly used diagnostic/treatment approach that is currently recognized as being effective for the proposed subjects' disease or condition, and that will be withheld from subjects assigned to the placebo arm of this research study:**
No - subjects assigned to the placebo and experimental arms of the research study will continue to undergo a commonly used diagnostic/treatment approach

2. **Describe the commonly used diagnostic/treatment approaches that will be withheld from subjects assigned to the placebo arm of this research study:**
No commonly-used treatment approach will be withheld from the subjects assigned to the placebo arm of this research study.

3. **Is enrollment into this study limited to individuals in whom the commonly used diagnostic/treatment approaches are known to be ineffective or intolerable?**
Enrollment into this study is limited to individuals who are opioid tolerant and therefore difficult to treat regarding post operative pain management. Subjects in both arms will receive the same standard of care treatment for post-operative pain management.

4. **Provide a scientific justification for the placebo-control arm of this research study:**
The placebo-control arm will allow for the clinicians to remain blinded to the treatment allocation of participants which will greatly improve the value of the pilot. This research is intended to develop an intervention (continuous, low dose ketamine infusion for 48 hours post-op) that can be implemented in the population from which trial participants are drawn (Opioid tolerant patients). Further, this trial does not require participants to forgo treatment they would otherwise receive

5. **How long will subjects participate in the placebo arm? Justify why this duration is necessary:**
Subjects randomized in the placebo arm will receive the saline placebo in the exact same fashion as the intervention arm--intraoperatively and then for 48 hours post-operatively.

6. **How frequently will the subject's condition or disease be monitored and compare that to the frequency of monitoring associated with standard care for this disease/condition?**
Participants in both groups will be monitored by the research team while in the hospital for incidence of adverse events, so they will be monitored more frequently than the standard of care.

7. **What specific endpoints will result in discontinuing a subject's participation due to worsening of the subject's disease or condition?**
The same stopping criteria for the intervention arm will be applied to the placebo arm, because clinicians will be blinded to treatment allocation.

8. **What is the risk to subjects who receive no active treatment for their disease or condition while in the placebo arm?**
Subjects in the placebo arm will still have their post-operative pain managed as per standard of care for this population at Presbyterian Hospital.

9. **Describe the planned involvement of a 'contact person' who interacts with the subject on a regular basis and who will notify the investigators immediately of any problems related to the subject's disease or condition:**
The study coordinator (Amy Monroe) will be monitoring the subjects on a regular, daily basis and will notify the PI of any problems related to the subject's condition.

Note: The involvement of the contact person must also be addressed in the consent form

View: Pitt SF: Conflict of Interest

Conflict of Interest

1. * **Is this an** FDA Covered Clinical Study**?**
(•) **Yes** ( ) No

Answer YES if it is:

- *A study of a drug or device in humans to be submitted in a marketing application or reclassification petition that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product); or*
- *A study in which a single investigator makes a significant contribution to the demonstration of safety.*

Do NOT include:

- *phase I tolerance studies or pharmacokinetic studies;*
- *clinical pharmacology studies (unless they are critical to an efficacy determination);*
- *large open safety studies conducted at multiple sites;*
- *treatment protocols; or*
- *parallel track protocols.*

2. * **Does this study involve a Non-Significant Risk Device and you anticipate including the results as part of any type of submission to the FDA for approval of this device?**

○ Yes ◉ **No**

3. * **Does any investigator involved in this study have a financial interest as the inventor or developer of intellectual property that is being evaluated or developed in this study including, but not limited to, a patent, trademark, copyright or licensing agreement?**

○ Yes ◉ **No**

4. * **Is this study funded in part or whole by a PHS Agency?**

○ Yes ◉ **No**

5. * **Does any investigator involved in this study (select all that apply):**

☐ A. Have a financial interest (aggregated value of equity and remuneration during the past or next twelve months) in a publicly-traded entity that either sponsors this research or owns the technology being evaluated or developed that exceeds a 5% ownership interest or a current value of $10,000?

☐ B. Receive remuneration (during the past or next twelve months) from a non-publicly traded entity that either sponsors this research or owns the technology being evaluated or developed that exceeds $10,000?

☐ C. Have equity in a non-publicly traded entity that either sponsors this research or owns the technology being evaluated or developed?

☐ D. Have rights as either the author or inventor of intellectual property being evaluated or developed in this research and for which you are receiving royalties,

	milestone fees, or other proceeds that have or will exceed $10,000 in any 12-month period (include payments through the University of Pittsburgh, the Veterans Administration Pittsburgh Healthcare System, UPMC, and University of Pittsburgh Physicians)?
☐	E. Have an officer or management position with a company that either sponsors this research or owns the technology being evaluated or developed?
☐	F. Receive compensation of any amount when the value of the compensation would be affected by the outcome of this research, such as compensation that is explicitly greater for a favorable outcome than for an unfavorable outcome or compensation in the form of an equity interest in the entity that either sponsors this research or owns the technology being evaluated or developed?
☑	**None of the above options apply and there are no other financial conflicts of interest in the conduct of this research.**

6. **Provide the name of the investigator(s) and describe the nature of the Significant Financial Interest(s):**

View: Pitt SF: Ancillary Reviews

Ancillary Reviews

1. **Ancillary reviews or notifications selected below are required based on previous answers to questions. If a selection is incorrect, return to the appropriate page and adjust the answers to questions on that page:**

- ☐ **Conflict of Interest (COI)**
- ☐ **Clinical and Translational Research Center (CTRC)**
- ☑ **Data Security**
- ☐ **Honest Broker**
- ☑ **UPMC Investigational Drug Service**
- ☐ **Pitt Medical School Review**

- [ ] Office of Investigator-Sponsored IND & IDE Support (O3IS)
- [ ] RCCO Business Manager (required for industry sponsored studies)
- [ ] Religious Directives
- [x] Scientific Review
- [x] Health Record Research Request (R3) (required if using UPMC clinical data and authorization for other UPMC data sources for research)
- [x] UPMC Office of Sponsored Programs and Research Support (using UPMC facilities and/or UPMC patients during the conduct of the study)

2. **Additional ancillary reviews the PI may choose to include as needed for the research:**

- [ ] Human Stem Cell Oversight (hSCRO)
- [ ] Institutional Biosafety Committee (IBC)(study involves deliberate transfer of recombinant or synthetic nucleic acid molecules)
- [ ] Radioactive Drug Research Committee (RDRC)(study involves the evaluation or use of procedures that emit ionizing radiation)

View: Pitt SF: Clinical Trials

Good Clinical Practice (GCP) Training

1. * **Regardless of funding source, is this study a clinical trial (as defined by the NIH)?**
   (•) **Yes** ( ) No

ClinicalTrials.gov Information

Visit the University of Pittsburgh Office for ClinicalTrials.gov website or contact ctgov@pitt.edu for further information.

2. * **Was this study registered, or will it be registered, on ClinicalTrials.gov?**
   (•) **Yes** ( ) No
3. * **Is the University of Pittsburgh or UPMC the Sponsor Organization for this study record?**
   (•) **Yes** ( ) No

* **Who will be the Responsible Party for this study record?**

Principal Investigator of this IRB application

View: Pitt SF: Supporting Documents

Supporting Documents

1. **Attach any additional supporting documents not previously uploaded. Name the documents as you want them to appear in the approval letter:**

Document	Category	Date Modified	Document History
There are no items to display			

View: Pitt Create

Add Drug Information

1. **Select the drug:**
   Ketamine

If you cannot find the drug in the list above, enter its information here:

Generic name:

Brand name:

2. * **Purpose of their use:**
KETALAR (generic: ketamine) is a rapid-acting general anesthetic producing an anesthetic state characterized by profound analgesia, normal pharyngeal-laryngeal reflexes, normal or slightly enhanced skeletal muscle tone, cardiovascular and respiratory stimulation, and occasionally a transient and minimal respiratory depression. The mechanism of action is primarily due to antagonism of N-methyl-D-aspartate (NMDA receptors) in the central nervous system.

3. * **FDA status:**
Drug being used "off-label"

4. **Attach files related to this drug:**

	Document	Category	Date Modified	Document History
View	memo signed.pdf(0.01)	Drug Attachment	2/12/2019	History
View	FDA exempt.pdf(0.01)	Drug Attachment	2/12/2019	History
View	Ketamine package insert.pdf(0.01)	Drug Attachment	2/12/2019	History

5. **Attachments may include a copy of the package insert, investigator brochure, product labeling, or verification of any IND number.**

View: Pitt Create

Add Storage Information

1. * **Select a Storage Type:**
UPMC owned desktop, laptop or other device

2. **Description:**

3. * **Will identifiable data be stored in this location?**
   ○ Yes ◉ **No**

4. * **Will sensitive data be stored in this location?**
   ○ Yes ◉ **No**

5. **Will de-Identified or anonymous data be stored in this location?**
   ○ Yes ◉ **No**

6. * **Is anti-virus software installed and up to date on all devices and are the operating systems kept up-to-date on all devices?**
   ◉ **Yes** ○ No

7. **Provide additional information as needed:**

View: Pitt Create

Add Storage Information

1. * **Select a Storage Type:**
   Server: UPMC Managed Server
2. **Description:**

3. * **Will identifiable data be stored in this location?**
   ◉ **Yes** ○ No

4. * **Will sensitive data be stored in this location?**
   ◉ **Yes** ○ No

5. **Will de-Identified or anonymous data be stored in this location?**
   ◉ **Yes** ○ No
6. **Provide additional information as needed:**

View: Pitt Risk

Risk

1. * **Research Activity:**
   Collection of information from medical records
2. **Common Risks:**
3. **Infrequent Risks:**
   Breach of confidentiality
4. **Other Risks:**

View: Pitt Risk

Risk

1. * **Research Activity:**
   completion of questionnaires
2. **Common Risks:**
3. **Infrequent Risks:**
   feelings of frustration, embarrassment or boredom
4. **Other Risks:**

View: Pitt Risk

Risk

1. * **Research Activity:**
   low dose ketamine infusion

2. **Common Risks:**

3. **Infrequent Risks:**
   Allergic Reaction (rare) Blurred vision(infrequent) Confusion (infrequent) Drowsiness (infrequent) Increased or decreased blood pressure or heart rate (infrequent) Mental or mood changes (infrequent) Nausea and vomiting (infrequent) Dreams, hallucinations and delirium (infrequent) Liver injury (rare)

4. **Other Risks:**
   With respect to the risk of liver injury, there have been reports of reversible, elevated liver enzymes associated with long term, repetitive use of high dose ketamine, although there are currently no reports of liver injury associate with low dose ketamine, which is used in this study. That being said, you are instructed to notice the following signs and symptoms of liver injury, and report to physicians with the information of previous exposure of ketamine infusion:
   • Discolored skin and eyes that appear yellowish
   • Abdominal pain and swelling
   • Itchy skin that doesn't seem to go away
   • Dark urine color
   • Pale stool color
   • Bloody or tar-colored stool
   • Chronic fatigue
   • Nausea
   • Loss of appetite

View: Pitt Risk

Risk

1. * **Research Activity:**
   cold pressor test

2. **Common Risks:**

3. **Infrequent Risks:**
   Excessive painful sensation (rare)
   tissue damage (rare)

4. **Other Risks:**