Cover Page

NMCCL.2018.0011

31Jan2024

“Impact of Ketamine on the Acutely Suicidal Patients in the Emergency Department”

EIRB Protocol Template (Version 1.7)

1.0 General Information

***Please enter the full title of your study:**

Impact of Ketamine on the Acutely Suicidal Patients in the Emergency Department

***Please enter the Protocol Number you would like to use to reference the protocol:**

NMCCL.2018.0011
* This field allows you to enter an abbreviated version of the Protocol Title to quickly identify this protocol.

Is this a multi-site study (i.e. Each site has their own Principal Investigator)?

No

Does this protocol involve the use of animals?

○ Yes ◉ No

2.0 Add Site(s)

2.1 List sites associated with this study:

Primary Dept?	Department Name
◉	**Navy** - Naval Medical Center Camp Lejeune (NMCCL)

3.0 Assign project personnel access to the project

3.1 *Please add a Principal Investigator for the study:

Butler, Nathan Henry, DO, MBA

Select if applicable

☐ Student ☐ Site Chair
☐ Resident ☐ Fellow

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

Jolicoeur, Amy N, BSN
Associate Investigator

B) Research Support Staff

BURTON, SARAH BETH
Team Member
CHRISTIAN, CATHERINE Catlett
Research Coordinator
Cisneros, Kylee Joelene, MSN
Monitor
Nottingham, Kole KONNER DEAN
Team Member

3.3 *Please add a Protocol Contact:

CHRISTIAN, CATHERINE Catlett

The Protocol Contact(s) will receive all important system notifications along with the Principal Investigator. (i.e. The protocol contact(s) are typically either the Protocol Coordinator or the Principal Investigator themselves).

3.4 If applicable, please select the Designated Site Approval(s):

Add the name of the individual authorized to approve and sign off on this protocol from your Site (e.g. the Site Chair).

4.0 Project Information

4.1 * Has another IRB/HRPP reviewed this study or will another IRB/HRPP be reviewing this study? If Yes, answer the questions according to the IRB/HRPP Determination.

○ Yes ◉ No

IRB Name	Review Date	Determination
No records have been added		

4.2 * Is this a research study or a Compassionate Use/Emergency Use/HUD project?

◉ Yes ○ No

4.3 What type of research is this?

- ☑ Biomedical Research
- ☐ Clinical trial (FDA regulated)
- ☐ Behavioral Research
- ☐ Educational Research
- ☐ Psychosocial Research
- ☐ Oral History
- ☐ Other

4.4 Are you conducting this project in pursuit of a personal degree?

○ Yes ◉ No

4.6 * Is this human subjects research? (As defined by 32 CFR 219) Human subject means a living individual about whom an investigator (whether professional or student) conducting research:
(i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
(ii) Obtains, uses, studies, analyzes or generates identifiable private information or identifiable biospecimens.

◉ Yes ○ No

4.7 * Do you believe this human subjects research is exempt from IRB review?

○ Yes ◉ No

5.0 Personnel Details

5.1 List any Research Team members without EIRB access that are not previously entered in the protocol:

No records have been added

5.2 Will you have a Research Monitor for this study?

◉ Yes
○ No
○ N/A

Research Monitor Qualifications
Ensure the individual has expertise consistent with the nature of risk(s) identified within your study and is independent of the team conducting the research.

Research Monitor Role:

The protocol for **Impact of Ketamine on the Acutely Suicidal Patients in the Emergency Department** will be considered "greater than minimal." For this reason, the below stated individual has been appointed as research monitor.

A research monitor has the expertise commensurate with the nature of risk(s) identified within the research protocol and must be independent of the investigative team. For this investigation, the research monitor will
serve concurrently as the ombudsperson if there is a misalignment in wishes between the subject and their LAR. The Human Subjects Protections Unit (HSPU) team member who is monitoring the informed consent process will complete a capacity assessment.

To appropriately act as research monitor, the monitor may discuss the research protocol with the investigators, interview study subjects, and consult with others outside of the project about the research.

Duties
The research monitor will perform **oversight** functions. This will encompass the following duties:

1. Observation of recruitment, enrollment, and consenting.
2. Monitor the study intervention and interaction between investigators and subjects.

3. Examine monitoring plans and reports and review data matching, collection, and data analysis procedures.

Authorities

In the event a problem is identified, the monitor will have the authority to stop a research protocol, remove individual subjects from a study, and take whatever steps are necessary to protect the safety and well-being of subjects until the IRB can assess the monitor's report.

The monitor is required to promptly report her medical monitoring and oversight monitoring observations and findings to the IRB or other designated official

If applicable, you may nominate an individual to serve as the Research Monitor:

Selected Users
Kylee Joelene Cisneros, MSN

6.0 Data/Specimens

6.1 Does the study involve the use of existing data or specimens only (no interaction with human subjects)?

○ Yes ◉ No

7.0 Funding and Disclosures

7.1 Source of Funding:

Funding Source	Funding Type	Amount
No records have been added		

Total amount of funding:

7.2 Do you or any other Investigator(s) have a disclosure of a personal interest or financial nature significant with sponsor(s), product(s), instrument(s) and/or company(ies) involved in this study?

○ Yes ◉ No

If Yes, complete and attach Conflict of Interest forms for all key personnel

8.0 Study Locations

8.1 Is this a collaborative or multi-site study? (e.g., are there any other institutions involved?)

○ Yes ◉ No

8.2 Study Facilities and Locations:

	Institution	Site Name	Site Role	FWA or DoD Assurance Number	Assurance Expiration Date	Is there an agreement?	IRB Reviewing for Site

No records have been added

Other:

	Other Institution Site	Site Role	FWA or DoD Assurance Number	FWA or DoD Expiration Date	Is there an agreement?	IRB Reviewing for Site
No records have been added						

8.3 Are there international sites?

Attach international approval documents, if applicable, when prompted. Note: Ensure local research context has been considered

○ Yes ◉ No

8.4 Is this an OCONUS (Outside Continental United States) study?

○ Yes ◉ No

Select the area of responsibility:

Have you obtained permission from that area of responsibility? (This is a requirement prior to study approval)

○ Yes ○ No

9.0 Study Details

9.1 Key Words:

Provide up to 5 key words that identify the broad topic(s) of your study

Suicidal Ideation
Ketamine
Infusion
Emergency Department
Military

9.2 Background and Significance:

Include a literature review that describes in detail the rationale for conducting the study. Include descriptions of any preliminary studies and findings that led to the development of the protocol. The background section should clearly support the choice of study variables and explain the basis for the research questions and/or study hypotheses. This section establishes the relevance of the study and explains the applicability of its findings

Suicide is the 10th leading cause of death in the United States.1 Worldwide, it is the 17th leading cause of death, taking 800,000 lives each year.10 Suicide is a serious public health problem with a complex and multidimensional etiology. The risk of suicide increases with age, as well as having a history prior attempts, a history of psychiatric disorders,1 and with military service11. Furthermore, SI is increased after the first month of starting an antidepressant.12 As of 2010, suicide is the 2nd leading cause of death among military personnel.2 Interestingly, most active members who committed suicide were never deployed. The Armed Forces Health Surveillance Center (AFHSC) reported the demographic who committed tended to be white, male, and active component members.2 This is similar to the general population who present to the ED with SI, who tend to be male, and between 18-64 years old.3 Soldiers with a history of behavioral health disorders have a higher suicide rate. Overall, there is an acute increase in suicide and suicide rates in military

members. 2 Despite increased number of medications and therapy modalities in psychiatry, the rate of suicide remains constant.9

Although the Navy has a lower suicide rate compared to other branches, this study is relevant to the Navy because it addresses a vital public concern which affects the lives and families of their service members. Also, Navy medicine takes care of any member or dependent of any branch of the military, not just sailors. There is a general lack of validated and effective intervention to prevent suicide in not only the military, but also the civilian population. 2

Over the last three-decades, Emergency Medicine (EM) has seen a 12% annual average increase in the number of visits due to attempted suicide.3, 4 This profound increase has forced many ED staff members to be the first point of contact for acute mental health care.4 Although mental health and substance dependence diagnoses increases an individual's risk for suicide, 37% of those who did not have these comorbidities visited the ED within a year of death from suicide.13 The ED has been identified as a vital component of suicide risk identification, support, and management.14 However, after discharge from the ED, as many as 70% of civilian patients do not attend their first outpatient appointments.15 This observed behavior follows from the idea that SI is associated with cognitive rigidity.16 Suicidal patients may not be mentally or emotionally motivated towards the safety planning17, patient education17, or efforts directed towards saving their life. The days immediately after discharge from the ED or psychiatric unit are a high-risk period17, and this elevated risk can last as long as a month.14

"Boarding" of psychiatric patients is an enormous and growing problem due to limited capacity for inpatient psychiatric care. Boarding is the practice of holding the patient in the ED while waiting for an open inpatient mental health bed. Studies cite an average of a seven hour wait for a bed following the decision to admit, which is extended if transfer to an outside facility is required.6-8 The boarding of psychiatric patients is 3.2 times longer than non-psychiatric ED patients. For each psychiatric patient awaiting inpatient care, there is a loss of 2.2 ED bed turnovers, which equates to $2,250 loss in payments and delay in care. This "healthcare system quality failure," is evidenced by an increased morbidity and mortality in not only the psychiatric, but other patients in need of emergent attention. The quick paced, busy, and chaotic environment of the ED can exacerbate psychological stress.18 This can negatively affect the psychiatric patient because leaving prior to screening and treatment increases the risk of self-harm and suicide.19 Furthermore, a lack of prospectively validated screening tools and scarcity of qualified professionals, especially during off hours, contribute to this phenomenon. 20

Current treatment for the acutely suicidal patients are limited to hospitalization, psychotherapy, ECT, or a combination of the aforementioned.5 However, as previously discussed, this has added to the national boarding problem. Long term pharmacologic treatment for suicidal behaviors and mood stabilization has been studied in specific populations. In these populations, the decreases in suicidal ideation results from stabilization of the underlying psychiatric illness. For example, Lithium has been used in mood disorders and Clozapine in schizophrenic patients.20 In those with mood disorders, cognitive behavioral therapy (CBT) and dialectical behavioral therapy (DBT) have shown to decrease deaths and rate of attempts long term.22,23

Irrespective of this psychiatric disease, suicidal thoughts alone represent a huge morbidity, and approximately 5.6% of the US population suffers from this. There are no drugs indicated for the treatment of immediate suicide risk.9 There exists initial support for the safety and tolerability of ketamine as an intervention for SI.9 Various recent studies have shown ketamine, at low doses, to have a rapid transient antidepressant and anti-suicidal effects. This off-label use has a B level of Evidence.25 Due to the urgent need for effective therapy, the FDA granted IV esKetamine, a form of ketamine, "Breakthrough therapy" status in both 2013 and 2016 to expedite its development in the treatment of those with major depressive disorder. Results of Phase three data demonstrate ketamine's ability to reduce depressive symptoms. To date, outcomes of ketamine's utility in addressing immediate risk of suicide is unknown.9

Historically, Ketamine is most commonly used as an anesthetic with analgesic properties. Recently, it has been used off-label for pain management, procedural sedation, status epilepticus, and treatment resistant depression. 25 Furthermore, it has been demonstrated that a single dose of IV ketamine is a safe and generally well-tolerated intervention for patients with chronic PTSD. 26 Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, is most commonly metabolized to Norketamine, which shows up in the blood within two to three minutes, and peaks at 30 minutes.28 In addition to NMDA receptors, Ketamine, also, binds to the opioid, monoaminergic, cholinergic, nicotinic, and muscarinic receptors. By stimulating adrenergic neurons and preventing catecholamine uptake, through the monoaminergic system, it increases norepinephrine (NE), dopamine, and serotonin. An increase in theses neurotransmitters (NT) is similar to the effects of anti-depressants. In continuation, these NT are central players in the serotonergic system, noradrenergic system, and the hypothalamic-pituitary-adrenal (HPA) axes, which all have been identified as abnormal in suicide and attempted suicide individuals.30

There is a strong corollary between stress and the development of depression and suicidal behaviors.30,31 The neurobiological mediators of stress are primarily controlled by the noradrenergic and corticotropin-releasing factor (CRF) median eminence systems. Furthermore, stress directly and indirectly, through the HPA axis, activates the Locus Coeruleus (LC), which is the primary producer of NE in the central nervous system (CNS). Directly, glutaminergic neurons send

excitatory signals to the LC via interaction with NMDA receptors 32 NMDA antagonists, such as ketamine, can dampen the glutaminergic system, which has been implicated during states of depression and low moods. 33

The neurobiological commonality between multiple psychiatric disorders and depression, suicide, and attempted suicide is a decrease in serotonergic activity.34 It has been shown that patients who died of suicide, have decreased serotonin transporter in the ventromedial prefrontal cortex and anterior cingulate, which are areas that control decision making or willful action. The prefrontal cortex is important for inhibitory behavioral control. A potential treatment modality of ketamine, is that it produces activation of this region.35 The anterior cingulate cortex has been shown to be associated with impulsive aggression compared to control. Clinical studies have shown that low CSF 5-HIAA, metabolite in serotonin system, has been implicated and positively correlated to aggression scores and impulsivity.30 This is interesting because, suicides in the military are thought to have an impulsivity component, triggered by one or more major life stressors. 2

Another region associated with suicide is the infralimbic cortex. A recent study, based on neuroimaging techniques, demonstrated that glucose metabolism in this region was associated with SI at baseline, and decreases in SI was observed after ketamine infusion. This is the same region target by deep brain stimulation, for depression treatment. Additionally, the infralimbic cortex has been implicated in behavioral flexibility. Implicating that ketamine's anti-suicidal properties may stem from its ability to promoting cognitive flexibility.33 Most likely due to its ability to increase brain-derived neurotrophic factor (BDNF), which is a major contributor to neuronal plasticity. BDNF also plays key roles in synaptic and long-term potentiation, which may counteract the decreased levels in MDD patients.36 Furthermore, ketamine infusion has been shown to change sleep slow wave activity.37 This biomarker is functionally related to increased synaptic strengthening and cortical synchronization.34 These factors, combined, may be implicated in not only ketamine's antidepressant effects and counteraction of decreased synaptic plasticity seen mood disorders,36 but also its ability to have week long lasting effects.24

This information leads us to hypothesize that treatment of acutely suicidal patients with ketamine would: 1) decrease SI to a clinically significant degree, and 2) the effect of ketamine will be seen for as long as one-week post administration.

To the best of our knowledge, this study does not duplicate any ongoing work. Instead, it would strengthen power to past studies and current work. There are four clinical trials investigating ketamine's effect on SI. One has an unknown status. There are two that are investigating ketamine in relationship to psychiatric standard of care, whereas this study is investigating its effects against a saline placebo. Finally, the last clinical trial is investigating the Neurobiology of Suicide. Their phase 2 component, which utilizes a similar protocol, uses ketamine as a tool to identify potential biomarkers for suicide.39 Furthermore, this study differs from Janssen Research & Development's clinical trial in administration route and study design. Their study focuses on using ketamine through intranasal administration. Their primary outcomes are the long-term safety and efficacy, and the design of their study is an open label multicenter trial.9

This research does not duplicate any prior work. To date, there is only one study, from Iran, that evaluates the effectiveness of ketamine in high risk patients, or those that present as acutely suicidal to the ED. This was a single blinded trial that utilized 0.2mg/kg infused over one minute. The study indicated significant decrease in their measurement outcomes. However, they concluded that ketamine is not a good choice for treatment because it did not meet their cut off values. Their results might have been influenced by the rapid infusion over one minute, which differs from our study as well as the vast majority of the literature. We believe the slower 40-minute infusion is necessary for optimal results, as the larger dosage has produced more clinically meaningful results in prior studies, and the slower infusion produced less negative side effects.41 They chose the minimal dose shown to diminish SI41 200 ng/ml (0.2 mg/kg), which provokes lateral nystagmus.35 This protocol utilizes a higher dose, 0.5 mg/kg, which is the ED50 for narcosis. Our study is medically relevant because dosage effects on SI have not been studied. Comparison of our studies may address questions regarding the optimal dose and infusion rate.

The BSSI will measure the severity of SI. It is based on the interviewer rated version of the original Scale for Suicidal Ideation (SSI), which is one of the few document suicide assessment tools with predictive validity for suicide completion.42 The internal reliability, test and retest validity, as well as invariance over time has been demonstrated for the BSS. 43, 45Furthermore, the first five items of the BSSI are a common clinical screening for the presence of suicidal thoughts.40 For these reasons, the BSSI was chosen as our primary outcomes measure. Two studies have indicated that the cut off between high and low risk is a BSS ≥ 2.43, 45 A recent investigation has determined BSSI ≥ 6 is predictive of future suicide attempts. 53 These two values will serve in our analysis.

The Montgomery– Åsberg Depression Rating Scale (MADRS) is a widely known 10 item clinician administered measure of depression severity.46 Since it's development in the late 1970s, it has become more popular than the gold standard, Hamilton rating scale for Depression (HAM-D). It is considered to be more sensitive to change, just as effective, and simpler to use clinically.47 However, the reliability depends on good interrater agreement.48 Difficulties in clinical trial to show signal detection for known effective drugs have implicated clinician administered measurement as a possible source of error. To avoid poor interrater reliability, rater bias, and variable interview quality,48 this trial will utilize the self-administered version of the MADRS-S.49 This has 9 items and

a total score ranging from 0 to 27.50 The scoring of MADRS-S has shown to be similar to that of physician scoring.51

The emotional pain of the suicidal patient requires empathetic care52 that may not always be possible with the time pressures, volume, and pragmatic nature of the ED environment. A pharmacologic intervention with rapid effects to decrease SI would play a vital role in improving the standard of care for this vulnerable population.53

9.3 Objectives/Specific Aims/Research Questions:

Describe the purpose and objective(s) of the study, specific aims, and/or research questions/hypotheses

Suicide is a leading cause of death worldwide.[1] In the United States, this national problem has profound effects in not only the civilian, but also the military population.[2] Over the last few decades, the Emergency Department (ED) has seen an increase in visits due to attempted suicide.[3,4] Current treatment for the acutely suicidal patients are limited to hospitalization, psychotherapy, ECT, or a combination of the aforementioned.[5] However, this adds to the national problem of boarding psychiatric patients. In the ED, this poses a danger and adds to the complexity revolving around management of the suicidal patient.[6-8] Despite increased number of medications and therapy modalities in psychiatry, the rate of suicide remains constant.[9] A growing body of research has implicated ketamine's antidepressant and anti-suicidal properties.[9] So much so that, the FDA has granted Janssen's esKetamine, a derivative, breakthrough drug status for treatment resistant depression. However, there is still no drug indicated for the treatment of immediate suicide risk

Problem statement: There is a general lack of validated and effective pharmacologic interventions for the treatment of suicide in not only in the military, but also the civilian population. To date, outcomes of ketamine's utility in addressing immediate risk of suicide is unknown.[9] Rapid acting pharmacologic intervention for the acutely suicidal patient, although necessary, suffers from a lack of critical studies.

Primary outcome:

Specific aim 1: The objective of this investigation is to identify the clinical effectiveness of sub-dissociative dose IV Ketamine as an adjunctive treatment for the acutely suicidal patient in the ED.
Hypothesis 1: There will be a clinically significant decrease in suicidal ideation (SI) in those treated with Ketamine after 24 hours.

Secondary outcomes:

Specific aim 2: Determine if this protocol for ketamine holds its effectiveness over time post infusion.
Hypothesis 2: The effects of ketamine can last up to a week post infusion.

Primary outcome measures of SI will be through self-administered Beck Scale for Suicidal Ideation (BSS or BSSI or SSI). The self-administered version of Montgomery– Åsberg Depression Rating Scale (MADRS) will be used to measures degree of concomitant depression symptoms. These patient-level data will serve as baseline comparatives. Subjects shall be randomized by the pharmacy and designated to either ketamine treated or saline placebo arm, with both the treating nurse and physician blinded. The experimental arm shall receive 0.5 mg/kg IV ketamine infusion over 40 minutes. To test for effectiveness within groups, we will measure outcomes at two different time points, 4 and 24 hours post infusion. To evaluate effectiveness between groups we will compare results between treatment and placebo arms. To test for specific aim 2, and to maximize response rate, a phone call will be made, one week after the initial questionnaire was done.

9.4 Study Design:

Describe study design in one to two sentences (e.g., prospective, use of existing records/data/specimens, observational, cross-sectional, interventional, randomized, placebo-controlled, cohort, etc.). Specify the phase – Phase I, II, III, or IV – for FDA-regulated investigational drug research

This study is designed as an RCT with two arms, Experimental vs. Placebo. Table 1 shows a detailed description of both arms. This will be a triple masked study. The patient, healthcare providers, and outcomes assessor will be blinded.

Table 1: Description of Experimental Arms

Arm	Intervention/Treatment
Experimental: Ketamine	Drug: Ketamine (Ketalar) Single dose IV ketamine, 0.5 mg/kg in 100 cc Normal Saline, infused over 40 minutes Other Name: N-methyl-D-aspartate (NMDA) glutamate receptor antagonist
Placebo: Saline	Drug: Normal Saline (NS) 100 cc infused over 40 minutes

9.5 Target Population:

Describe the population to whom the study findings will be generalized

Suicidal behavior is complex and affects all age groups, with the highest prevalence in those that are middle aged (45-54 years old). With this said it is the 4th leading cause of death in those 35 to 44 years old. <35 years old it is the second leading cause of death.1 Therefore, the selected subject population reflects any adult that could present to the ED. Children and adolescents (< 18 years old) are excluded to mitigate the variabilities their developing brain would introduce into the study.

9.6 Benefit to the DoD:

State how this study will impact or be of benefit to the Department of Defense

Suicide is an enormous burden on the active duty service member's operational readiness, as it has the potential to permanently take the member out of the fight. The rippling effects, of this individual action, not only affects moral of that sailor or marine's unit, but it also has profound impacts on the friends, coworkers, and, most importantly, their family. This study has the potential to provide additional intervention treatment literature.

10.0 Study Procedures, Data Management, and Privacy

10.1 Study Procedures:

Describe step-by-step how the study will be conducted from beginning to end

RESEARCH DESIGN/METHODS/SUBJECT JUSTIFICATION

General Approach
This study will be conducted in the ED. The investigative team will notify the ED that this research is underway. Emergency Department staff will be given an informational brief regarding the nature, purpose and scope of the research protocol. The brief will be distributed digitally via email, and will be discussed in staff meetings and huddles to reach 100% of staff. Healthcare personnel who wish to participate will be given a script and check list for exclusion criteria. If a physician feels that a patient may be eligible for participation he/she can refer the patient to the research team for additional evaluation and approach regarding the research study" The role of this individual is only for recruitment purposes and will not be involved in any other activities of the protocol or informed of patient information pertaining to the research.

Participants will be adults, whom are 18 years or older, military personnel or civilians eligible for care in the military treatment facility. This study aims to test for a clinically significant decrease in SI in the acutely suicidal patient. Repeat measures over time will be conducted at two subsequent

time points. To determine week long lasting effects of treatment, a third repeat measure will be conducted. All time point collections will be done for both arms.

The trial is designed as a double-blinded Randomized Control Trial (RCT) with two arms, Experimental vs. Placebo. This trial will mask patients, health providers, and outcome assessors to avoid ascertainment bias; the only unblinded participants will be the pharmacy, which will not affect the blinding, because at our institution they do not decide on patient disposition. This study design is not only necessary to demonstrate the effectiveness as a treatment for the acutely suicidal patient, but also to validate and add power to studies supporting anti-suicidal properties of ketamine. Outcomes will be measured by Psychometric testing (BSSI & MADRS-S). With the exception of the aforementioned experimental procedure, which will be done prior to transfer to inpatient units, both arms will then be treated in accordance to usual management for suicidal patients, which for both arms includes inpatient admission, therapy, and possible initiation of antidepressants.

Suicidal patients, subjectively identified by clinician, upon admission to the ED will be medically cleared by the EM physician, and then meet with the mental health liaison to be screened for admission to the psychiatric department, per normal standard of care. Study investigators will not be available around the clock, but when available will begin the pre-screening method for this investigation. The treating physician will pre-screen them for inclusion and exclusion criteria per an IRB approved check list (Appendix D: Criteria Checklist).

The patient will be approached for informed consent in accordance to with 21 CRF 50. They will be provided with a written document that embodies the elements of the informed consent. The consent will be presented orally to the subject with a witness. Once presented the subject will be given a reasonable time to review the contents and inquire information. Upon signing of the form, a copy shall be given to them.

Once consent is obtained, they will be presented with a paper form to complete the BSSI and MADRS-S. These measures will serve as baseline severity of suicidal wishes and plans, and degree of depression symptoms. Questionnaires will be stored in locked drawer's in the locked office the Division Officers in the Emergency Department, the Inpatient Mental Health ward, or the study coordinator.

Once the patient is deemed medically cleared by the treating physician, the study treatment will be ordered by an ED provider, per the randomization schedule, and administered by an ED nurse (Please see below for more detailed methodology). Those in the experimental arm will be treated with 0.5 mg/kg IV infusion of ketamine over 40 minutes. Those in the control arm will be treated with 100 cc Saline infusion over 40 minutes. (Table 1) Since there are no pharmaceutical treatment specific for acute suicide, it is in accordance to the Declaration of Helsinki (DOH) to utilize a saline placebo control. Vitals will be checked every 5 minutes during infusion. Questionnaires will be repeated at four time points for both arms, once in the ED before drug administration, one at 4 (+/-1) hours post-infusion, whether in the ED or the psychiatric unit, another 24-36 hours after the infusion in the inpatient psychiatric unit, and lastly one-week (+1 day) post treatment by phone call.

Research Objective

The primary objective of this investigation is to identify utility of Ketamine as a clinically effective and efficient adjunctive treatment modality for the acutely suicidal patient in the ED setting. Secondary objective is to investigate prospectively if the anti-suicidal effects are able to have lasting effect up to one week within the vulnerable period post discharge.

Detail How Many Groups or Arms are in the Study and what each Receives

This study is designed as an RCT with two arms, Experimental vs. Placebo. Table 1 shows a detailed description of both arms. This will be a triple masked study. The patient, healthcare providers, and outcomes assessor will be blinded.

Table 1: Description of Experimental Arms

Arm	Intervention/Treatment
Experimental: Ketamine	Drug: Ketamine (Ketalar) Single dose IV ketamine, 0.5 mg/kg in 100 cc Normal Saline, infused over 40 minutes Other Name: N-methyl-D-aspartate (NMDA) glutamate receptor antagonist
Placebo: Saline	Drug: Normal Saline (NS) 100 cc infused over 40 minutes

Randomization Procedures

Randomization will be done through permuted block randomization and stratified for history of mood disorder (e.g., major depression, bipolar disorder, dysthymia). Due to the small size of this study, block randomization will ensure an equal number of treatment and controls.52 Randomization can lead to unbalanced groups with respect to prognostic factor.52 Because 60% of those who commit suicide have a mood disorder, this study will be stratified by this prognostic factor.52 This computer-generated list,54 will provide a subject identifier. This list of subject identifier and procedure status will serve secondarily as an audit trail

Methods and Materials

All procedures in the management of the acutely suicidal patient will be in accordance with the standard of care, which includes a focused history and physical by an Emergency Medicine physician. Figure 1 demonstrates the flow of investigational procedures. The EM provider shall medically screen the patient and include appropriate ancillary studies. For example, if a patient is altered, intoxicated, sick-appearing, or exhibiting a clinical toxidrome, standard labs, EKG, or imaging will be ordered per standard of care. All female patients will have a urine HCG documented. Then, screening for admission to the psychiatric department will be done by the mental health liaison. This standard procedure will serve secondarily as the pre-screening method for this investigation. This will minimize duplication of work.

Once the patient is deemed "to be admitted to the psychiatric unit," the physician will check the Electronic Medical Records (EMR) for inclusion and exclusion criteria. If a patient's current medication has a possible interaction with ketamine, the ordering provider will consider consulting with the inpatient pharmacist about possible contraindications, which will be documented in the chart. Once screened as a potential subject for the study, the patient will be approached for consent. Consent explaining the research protocols, benefits, and risks will be obtained once by a member of the investigative team. Consent will be obtained from a clinically sober intervention-eligible patient, who is accepted to inpatient psychiatry. It will be obtained while in the ED. Subjects will consent on an individual basis. Consent will be documented on a standardized consent form approved by the IRB. Any female patient will undergo a pregnancy test to verify eligibility.

Once the patient is enrolled, the physician will calculate the dosage based on actual weight70,71 and place the order in the electronic medical record. The emergency department nurse assigned to the care of the patient will fax the order to the pharmacy. At this point, the pharmacy will follow the randomization instruction and schedule, and undergo three safety checks per pharmacy protocol. (Appendix D: Randomization List & Instructions.) The medication will be treated as a controlled substance and will require a nurse or clinician to pick it up from the inpatient pharmacy.

To attain a psychometric baseline, the patient will complete the BSSI and MADRS, on paper forms. After completion of baseline, the clinician will administer a single dose of IV ketamine, per experimental protocol procedure. The specific dose and route of administration were selected based on average dosage and administration from meta-analysis studies.5,41 A bolus of ketamine was another common route of administration. However, there is no statistical significance between this and the one selected.51 This study will not require any wash out periods or concomitant dosing regimens. This dosage and infusion regimen is not considered sedation.

During ketamine infusion, vitals will be checked q5min with serial pulse and blood pressure measurements, and patient will have continuous pulse oximetry (Pox), with all vitals connected to monitors at the nurse's and doctor's stations. In addition, an attendant will be present at all times as per suicidal patient protocol. Treatment will be stopped if pulse or systolic blood pressure increases > 25% of baseline, respiratory rate is sustained at < 7, Pox decreases below 92%, or if severe psychomimetic effects or agitation present.57

If treatment is stopped before completion for any reason, the patient will be dropped from the study, and their symptoms will be treated as per usual protocol of the physician. For instance, for severe psychomimetic effects and agitation, benzodiazepines such as midazolam could be considered. If a negative side effect occurs and treatment is stopped, it will be reported to the research monitor immediately.

Post assessment psychometric testing will be repeated at three time points for both arms. The first time point will be 4 hours post treatment, which is the standard time to evaluate acute response to ketamine.51 This may be collected in the ED or in the Psychiatric Unit. Subsequent questionnaires will be completed either in the ED or in the Psychiatric Unit. ED nurses giving report to the Psychiatric Unit will indicate that the patient is enrolled in the study, and give the time of administration of the study intervention and will indicate when the next questionnaire should be completed. Based on the literature, 24 hours post treatment, our second time point is when half of patients treated with a single dose of IV ketamine have shown reduction in SI.24

Finally, patients will perform psychometric tests, ideally, one-week post infusion. They will be called at their phone number on file. The follow up BSSI will be administered by a study evaluator.58 Forms will be filled out, placed in trial mailbox, data transferred onto spreadsheet.

Potential difficulties:

1. Continuation/Concomitant use of psychotropics influence the same neurotransmitter as ketamine, making it difficult to discern direct effects of ketamine.
2. Heterogeneity of patients, enhances generality, but reduces confidence in any conclusions drawn.
3. Difficulty lie inherently in treating those with mood instability and difficult-to-treat patients. a.) Those with mood disorders (BD & MDD) may metabolize ketamine differently[59]

Potential limitations

1. Sample size
2. Need for replication
3. Placebo effect
4. Enrollment is only available when eligible study personnel are present
5. Depression is a placebo-responsive illness.[60] Because suicide risk varies with the nature of depressive or mood disorder,[61] the placebo effect is uncertain. Increased placebo effect increases variance and poor signal detection.
6. Lack of translational studies, especially in neurobiology of suicide.
7. SI measures suicide risk. However, it does not measure other psychological constructs associated with increased suicidal risk, such as hopelessness.[61]
8. Lack of variety of outcome measure limits the study.
9. There is no established clinical biomarker predictor of ketamine.[62]

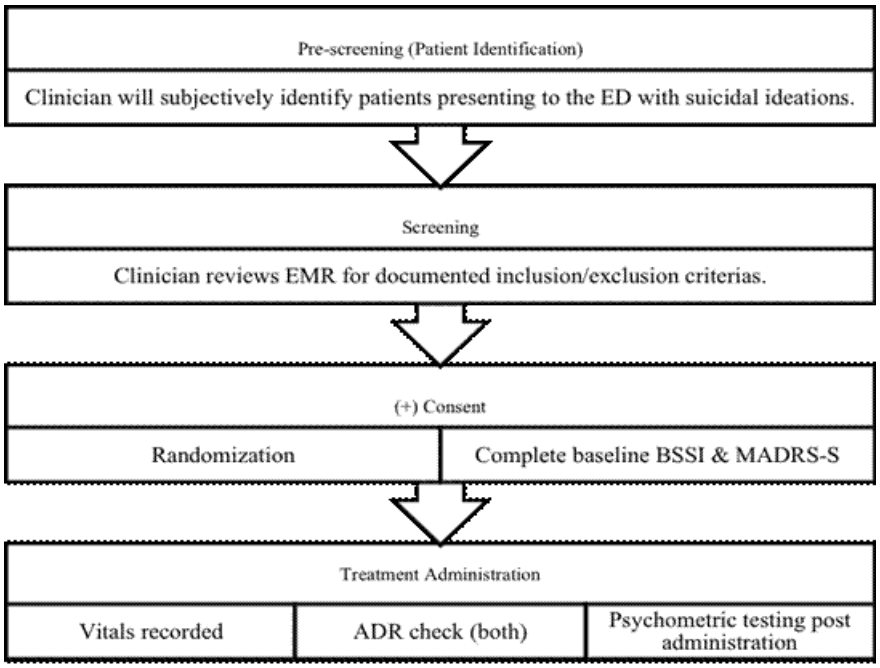

Figure 1: Flow of Experimental procedure

Experimental Procedure

1. Baseline evaluation of suicidal severity (BSSI) & degree of depressive symptoms (MADRS-S) will be evaluated through self-administered questionnaires.
2. The experimental and placebo arms will receive a single dose of IV ketamine, 0.5 mg/kg in 100 cc NS or 100 cc of NS infused over 40 minutes.
3. Post ketamine re-evaluation of outcome measures at four and twenty-four hours will determine clinical effectiveness of ketamine intervention
4. Inspection of admission and transfer time provides time measurement for LOS. This secondary measure is needed to determine efficiency of intervention.
5. Post ketamine re-evaluation of outcome measure at one-week post infusion will elucidate ketamine's durability of effect.

Table 2: Description of activities at time points during the study

	Study Visit 1 Baseline (t_0)	Study Visit 1 4 hours (t_1)	Study Visit 1 24 hours (t_2)	Study Visit 2 1 week (t_3)

Eligibility review and confirmation	X			
Education regarding research & Informed Consent signed	X			
History & Physical	X			
Randomization	X			
Dispense study drug	X			
IV Ketamine	X			
Vital Signs & ADR* monitored	X	X	X	
Review adverse events	X	X	X	
Psychometric testing	X	X	X	X

*ADR: Adverse drug reaction

10.2 Data Collection:

Describe all the data variables, information to be collected, the source of the data, and how the data will be operationally measured.

Research Material to Be Collected

1. The protocol requires patients to submit the following data:
    1. Phone number and email
    2. To measure SI severity, Self-administered BSSI (Appendix D: Sample BSSI)
    3. Level of depression shall be measured by the self-administered version of Montgomery-Åsberg Depression scale (MADRS-S). (Appendix D: MADRS-S)
2. The following information are obtained per standard of care, and will be collected through chart review:
    1. Medical history
        1. Psychiatric history
        2. Current and or Previous Diagnoses
        3. Current/recent antidepressant medication
        4. Current psychotropic medications
    2. Time stamps (admission & transfer)
3. The following additional information will be collected
    1. Class: military or civilian
    2. Number of previous suicide attempts
    3. History of self-harm
    4. Recent use of antidepressants
    5. Any applicable ancillary studies such as labs or imaging modalities
    6. Appendix D: Sample Data Collection Sheet
4. Identifier will be maintained in a spreadsheet that correlates subject identifier number and subject name. This will exist in privileged shared folder that only Investigators have permission to access. Data sheets will be coded such that only subject identifier numbers will exist on them.
5. Waiver of Authorization for the Use of PHI will not be necessary because request for access of medical history for research purposes is a component of the consent document. A separate authorization for the use of email in the one week follow up will also be requested at the time of consent.

Data Collection Tools

1. Pearson’s BSSI paper form
2. MADRS-SI paper form
3. EMR for chart review
4. Excel for data sheets

10.3 At any point in the study, will you request, use, or access health information in any form, including verbal, hard copy and electronic?

(•) Yes ( ) No

10.4 Review the definitions below and respond to the following two questions. If you are not sure of the answers, email DHA.PrivacyBoard@mail.mil for assistance. The *Military Health System (MHS)* is defined as all DoD health plans and DoD health care providers that are organized under the management authority of, or in the case of covered individual providers, assigned to or employed by, the Defense Health Agency (DHA), the Army, the Navy, or the Air Force *MHS workforce members* are employees, volunteers, trainees, and other persons whose conduct, in the performance of work for the MHS, is under the direct control of the MHS, whether or not they are paid by the MHS. *MHS business associates* are persons or entities that provide a service to the MHS and require protected health information (PHI) to provide the service.

Are you an MHS workforce member?

(•) Yes, I am an MHS workforce member
( ) No, I am not an MHS workforce member

Are you an MHS business associate?

(•) Yes, I am an MHS business associate
( ) No, I am not an MHS business associate

10.5 Have you consulted with an MHS data expert to determine the data elements required for your study?

Consulting with a data expert often saves time later in the compliance process because the data expert can advise on the data available in the numerous MHS information systems, the quality of that data and the methods for encrypting and collapsing data. To schedule a consult with an MHS data expert, send an email to: (**DHA.PrivacyBoard@mail.mil**)

( ) Yes, then complete the questions below according to the data consult
(•) No, then complete the questions below according to the best of your knowledge

10.6 Indicate how you will request data from the MHS. Select all that apply.

☑ Talking with MHS health care providers or MHS health plans about specific research participants
☑ Obtaining MHS hard copy records specific to research participants
☑ Obtaining data from an MHS information system(s)

10.7 If you are obtaining data from an MHS information system(s), indicate whether you plan to receive a data extract or whether you plan to access an MHS information system directly to create a data set.

A data extract is when the MHS or a contractor provides the data set directly to the researcher. When receiving a data set through data extract, the researcher may indicate whether the data elements should be provided as is, encrypted or collapsed. In contrast to a data extract, access to an information system means that the researcher may directly access an MHS information system and create a data set for the research study

☐ Data Extract
☑ Access

10.8 Do you intend to request de-identified data from the MHS in your research study?

There are different two methods for de-identifying data pursuant to HIPAA:
1) Safe Harbor Method: Removing all of the identifiers listed in Table 1 below, provided that the researcher does not have actual knowledge that the remaining data can be used alone or in combination with other information to identify the individual who is the subject of the information

2) Statistical Method: An expert, with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable, determines that the data is not individually identifiable

○ Yes ◉ No

10.9 Indicate the MHS information system(s) from which you will seek to obtain data

If you do not know which system(s) contains the data elements you need, refer to the Guide for DoD Researchers on Using MHS Data or request guidance from an MHS data expert at: **DHA.PrivacyBoard@mail.mil**.

Below is a list of commonly used MHS systems. If the system from which you seek to obtain data is not listed below, list the name of the system in the "Other MHS Systems" category below
PHI Systems:

MHS Information System	Requesting Data
: AHLTA	: Yes
: ESSENTRIS	: Yes

PII-Only Systems:

MHS Information System	Requesting Data

De-Identified Data & Other Systems:

Information System	Requesting Data
Other MHS System (May include PII and/or PHI) List other system here: T-SYSTEMS	: Yes

10.10 Do you intend to merge or otherwise associate the requested data with data from any sources outside of the MHS, including other DoD systems that are not part of the MHS?

○ Yes, will merge data
◉ No, will not merge data

10.11 Indicate the data elements about research participants or relatives, employers, or household members of the research participants that you will request from MHS hard copies or from MHS information systems.
If you will merge data, also indicate non-MHS data elements about research participants or relatives, employers, or household members of the research participants that you will have access to in any form or medium.

Data Element(s)	MHS	Non-MHS Systems	MHS Hard Copies
1. Names	☑	☐	☐
2. Postal address with only town, city, state and zip code	☐	☐	☐

3. Postal address with all geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of Census: 1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and 2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000	☐	☐	☐
4. Dates including all elements (except year) directly related to an individual, including birth date, admission date, discharge date, and date of death	☑	☐	☐
5. Ages over 89 and all elements of dates (including year) indicative of such age, unless you will only request a single category of "age 90 or older"	☐	☐	☐
6. Telephone numbers	☑	☐	☐
7. Fax numbers	☐	☐	☐
8. Electronic mail addresses	☑	☐	☐
9. Social Security numbers (SSNs)	☐	☐	☐
10. Medical record numbers	☐	☐	☐

11. Health plan beneficiary numbers	☐	☐	☐
12. Account numbers	☐	☐	☐
13. Certificate/license numbers	☐	☐	☐
14. Vehicle identifiers and serial numbers, including license plate numbers	☐	☐	☐
15. Device identifiers and serial numbers	☐	☐	☐
16. Web Universal Resource Locators (URLs)	☐	☐	☐
17. Internet Protocol (IP) address numbers	☐	☐	☐
18. Biometric identifiers, including finger and voice prints	☐	☐	☐
19. Full-face photographic images and any comparable images	☐	☐	☐
20. Any other unique identifying number, characteristic, or code (Diagnosis, DEERS ID, EDI-PI, Rank)	☐	☐	☐

If you are obtaining SSNs, provide a justification as to why and explain why a substitute cannot be used

10.12 Do you believe it is possible for the MHS data to become identifiable because of triangulation, a small cell size, or any unique data element(s)?

Triangulation means using different data elements that are not themselves identifiable but that when combined can be used to identify an individual. For example, triangulation would use rank and race together to determine the identity of an individual with a particular health condition.

Small cell size means that there is only a small number of eligible individuals that satisfy the category description. Guidance for acceptable cell size is available from the Centers for Medicare and Medicaid Services. For example, the rank category of four star generals with a particular

diagnosis may be less than 30, so the rank category may need to be expanded to include lower ranks.

A unique data element includes any unique features that are not explicitly enumerated in the categories of data in rows 1 – 20 of the table above (in Section 10.10), but that could be used to identify an individual. Unique data elements include characteristics that are not themselves identifying, such as the rank of general or admiral, or a race or gender, but within the context of other information could be identifiable.

- ○ Yes, I believe there is a reasonable possibility the MHS data will become identifiable
- ◉ No, I believe there is no reasonable possibility the MHS data will become identifiable

10.13 Have you completed and uploaded an appropriate HIPAA document (i.e. HIPAA Authorization will be obtained or Waiver/alteration of HIPAA Authorization is being requested)?

- ◉ Yes
- ○ No
- ○ N/A

10.14 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for this Study:

Include in this section the plan for acquiring data (both electronic and hard copy), access during the study, data/specimen storage and length of time stored, shipment/transmission, and the plan for storage and final disposition at the conclusion of the study. Describe any data agreements in place for accessing data within and/or outside of your institution (e.g., Data Sharing Agreement, Data Use Agreement, Business Agreements, etc.)

Protection and Security of Data and Identifying Information

1. Handling of paper questionnaires will be as follows:
    1. Questionnaires will be placed in trial mailbox.
    2. They will be kept in a locked box in a locked office, until they can be scanned into a secure digital folder.
2. Digital protection:
    1. Data will be stored in accordance to Navy HRPO policy and data storage policies
    2. Password protection: Each patient will be assigned a subject identifier during randomization. This file will be password protected.
        1. The data will remain on a study team member's computer which is only accessible with a CAC card.
    3. De-Identification: Only subject identifiers will be used in psychometric testing. Additionally, as shown in Figure 2, the subject identifier will be the only means to connect to various data related to the subject. The Subject identifier will be stored separate from all de-identified information.
    4. Separation of data: Data collection sheets will be separated into different files, as shown in Table 3.

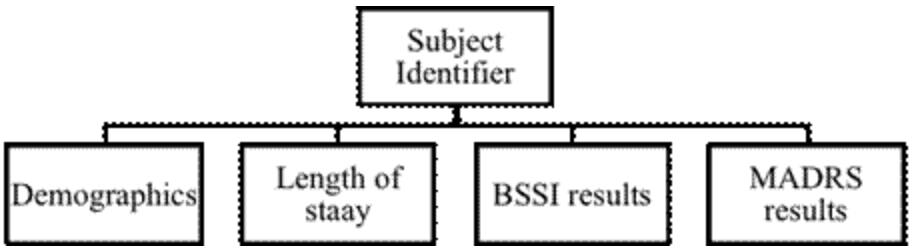

Figure 2: Subject Identifier connection to other data sheets for a participant

Table 3: Security Management breakdown of Data Collection Sheets

Spreadsheet	Contents	Who has access?	Security
Subject Identifier key	Subject identifier code & Patient name	NMCCL Investigators	Password protected
Demographics	Email, gender, DOB, age, number of previous attempted suicide, history of self-harm, psychiatric history,	Only Investigators	Separate file

	recent antidepressant use, current psychotropic medication, classification (military/civilian)		
LOS	Time of admission & transfer	Only Investigators	Separate file
BSSI	BSSI results	Only Investigators	Separate file
MADRS	MADRS results	Only Investigators	Separate File

(6) Disposition of Data and Identifying Information at End of Project

Specified data will be stored digitally in accordance to Navy regulation. All other documents will be disposed per Navy Instruction at the conclusion of the storage period. In accordance to DHHS protection of human subject's regulation, IRB activities and records will be maintained in digitally secure location for at least three years (45 CFR 46.115(b)). In accordance to HIPAA requirements, data that fall under this regulation will be stored for at least six years.

10.15 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for Future Research:

If the study involves collecting, storing, or banking human specimens, data, or documents (either by the Investigator or through an established repository) for FUTURE research, address. How the specimens/data will be used, where and how data/specimens will be stored (including shipping procedures, storage plan, etc.), whether and how consent will be obtained, procedures that will fulfill subjects' request as stated in the consent, whether subjects may withdraw their data/specimens from storage, whether and how subjects may be recontacted for future research and given the option to decline, whether there will be genetic testing on the specimens, who will have access to the data/specimens, and the linkage, the length of time that data/specimens will be stored and conditions under which data/specimens will be destroyed.

n/a

11.0 Statistical/Data Analysis Plan

11.1 Statistical Considerations:

List the statistical methods to be used to address the primary and secondary objectives, specific aims, and/or research hypotheses. Explain how missing data and outliers will be handled in the analysis. The analysis plan should be consistent with the study objectives. Include any sub-group analyses (e.g., gender or age group). Specify statistical methods and variables for each analysis. Describe how confounding variables will be controlled in the data analysis

STATISTICAL ANALYSIS
All data analysis will be carried out using SPSS ® Version 25. Tableau Desktop 2018.1 will be used to augment the creation of graphs. See 3.7.C for power calculation and sample size derivation. If subjects do not complete a baseline, they will not be incorporated in the analysis. A recent clinical study validated that an average of four items from the SSI, with a cut-off of ≥ 2, is sufficient in classifying patients as high risk vs. low risk.[61] Therefore, any patient who does not complete at least four items on the SSI during each of the post administration time points will be excluded from the study. Missing data will be excluded from analysis as long as the degree of freedom permits. The type of data analysis will be in accordance to the Test plan, Table 6. Each arm of the trial will be considered a "group." Appendix D: Sample Data Collection Sheet describes demographic data points as well as measurement scale of each of the below variables. Stratification factors will be accounted for as a covariate in multivariant models.[54]

11.2 Sample Size:

62

11.3 Total number of subjects requested (including records and specimens):

62

11.4 If you are recruiting by study arm, please identify the arms of the study and how many subjects will be enrolled in each arm

Experimental arm (Ketamine) - 31 subjects
Placebo arm (saline) - 31 subjects

11.5 Please provide a justification for your sample size

Number of Subjects and Justification

This trial aims to have a minimum of 62 individuals. N calculation was done using R's built in statistical power pack.[63] (Appendix D: N Calculation) Significance level and power used were the standard 0.05 and 0.8 respectively. Prior studies showed very large effect sizes. Their Cohen's d within groups and between groups were 1.23 and 1.45 respectively.[38] The power of a study depends on effect size as well as sample size. Because their effect size is sufficiently large, they are able to detect differences from even a small sample.

When using this effect size, N calculations resulted in 8.5 to 11.4 individuals, which correlates to 17 to 22.8 individuals. However, the design of our study varies from past studies, in that we include a broader patient population. Instead of simply at individuals diagnosed with a mood disorder.

Based on suggested Cohen's d values, in order to have a large effect size in the T-test and ANOVA tests, N should be 25.5. In order to determine large correlations, N needs to be at least 28.2. This correlates to 52 to 56 subjects. Applying an estimated 10% subject dropout rate, the estimated number of subjects needed for the study is 62. Full effect and sample size breakdown are shown in Table 4.

Table 4: Effect and Sample Size Breakdown

Test	Effect size	N
Two sample T-Test	Large (d =0.8)	25.5
Two sample T-Test	Medium (d = 0.5)	63.7
Two sample T-Test	Average within groups (d=1.23)	11.4
Two sample T-Test	Average between groups (d=1.45)	8.5
ANOVA	Large (f = 0.4)	25.5
ANOVA	Medium (f = 0.25)	63.7

A Linear model will be used for analysis of repeat measures if sample size reach 74 subjects. This model accounts for uneven spacing in repeated measures, accounts for random effects, will provide a greater flexibility in analysis.[64] The ability of this analysis is limited by the degree of freedom, which is influenced by the sample size. R separates the F test into two variables representing the degree of freedom of the model and error, which are the numerator and the denominators in the F test. In this test, the numerator (u) is the number of observations, and is equal to p -1, where p is the number of predictors (sex, age, etc.…). The denominator (v) is the degree of freedom of the error and is equal to n - p, where n is the number of observations, or, in our case, subjects.[64] Sample Calculation 1 was used to determine n need to power a model that would take into account three to five predictors. (Table 5)

Sample Calculation 1:

$u = p - 1 \rightarrow u + 1 = p$

$v = n - p \rightarrow v + p = n$

To solve for n:

$v + u + 1 = n$

Table 5: N needed to power Linear model with a large effect size (f2 = 0.35)

Numerator (u)	Denominator (v)	n	2n

5	37	43	86
4	34	37	74
3	31	35	70

11.6 Data Analysis Plan: Complete description: Background, Objectives, Design, Step by Step how the project is going to be done, Data analysis plan:

Table 6: Test Plan of Data Analysis

Question to be answered	Type of Analysis	Independent (x)	Dependent (y)	Relationship
Is there a difference effect of ketamine in those who are high suicide vs. high depressed?	McNemar test	High Suicide	High depressed	Within
Is there a difference in the placebo between the same two groups?	McNemar test	High Suicide group	High Suicide group	Within
Is there any difference between ketamine vs. placebo on BSSI & MADRS?	One-way MANOVA	Group	BSSI; MADRS	Between
Is there a difference in SI between Ketamine vs placebo	2 Independent sample t test	Group	BSSI @T4	Between
Is there a difference in depression between Ketamine vs placebo	2 independent sample t test	Group	MADRS @ T4	Between
Is there a difference in effect from placebo when accounting for covariates?	MANCOVA	Fixed factor: Group Covariates: Demographics	BSSI, MADRS @ T4	Between
Is there a difference in effect from ketamine @ the different time points?	**Mixed model** Or Repeated measure ANOVA	Fixed factor: Group	BSSI	Within & between
Is there a difference in group at the different time points, when MADRS is a covariate?	**Mixed model**	Fixed factor: Group Covariates: MADRS	BSSI	Within & between
Is there a difference in group at the different time points, when MADRS, and demographics are considered? *	**Mixed model**	Fixed factor: Group Covariates: MADRS, demographics	BSSI	Within & between

*This case requires a larger sample size.

12.0 Participant Information

12.1 Subject Population:

Participants will be adults, whom are 18 years or older, military personnel or civilians eligible for care in the military treatment facility.

12.2 Age Range:

Check all the boxes that apply. if the age range of potential subjects (specimens, records) does not match the range(s) selected, please specify in the text box.

- [ ] 0-17
- [x] 18-24
- [x] 25-34
- [x] 35-44
- [x] 45-54
- [x] 55-64
- [x] 65-74
- [x] 75+

12.3 Gender:

- [x] Male
- [x] Female
- [ ] Other

12.4 Special categories, check all that apply

- [ ] Minors /Children
- [x] Students
- [x] Employees - Civilian
- [x] Employees - Contractor
- [x] Resident/trainee
- [x] Cadets /Midshipmen
- [x] Active Duty Military Personnel
- [x] Wounded Warriors
- [x] Economically Disadvantaged Persons
- [x] Educationally Disadvantaged Persons
- [ ] Physically Challenged (Physical challenges include visual and/or auditory impairment)
- [ ] Persons with Impaired Decisional Capacity
- [ ] Prisoners
- [ ] Pregnant Women, Fetuses, and Neonates
- [ ] Non-English Speakers
- [ ] International Research involving Foreign Nationals - Headquarters Review is necessary

You must also consider the requirements of DoDI 3216.02, paragraph 7.e.

You must also consider the requirements of DoDI 3216.02, Enclosure 3, paragraphs 7.e. and 12.

You must also consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e.

Depending on your intended subjects' status, you may also need to consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e.

You must also consider the requirements of 32 CFR 219.111(b).

You must also consider the requirements of 32 CFR 219.111(b).

12.5 Inclusion Criteria:

Order Number	Criteria
1	Subject Inclusion and Selection Criteria 1. Patient demographics will consist of Active, Reserve, or retired military personnel or their dependents. Subjects must meet the following inclusion criteria: 2. Adult (18 to 89 years old) 3. Present with active SI 4. Deemed to being admitted to inpatient psychiatric unit

12.6 Exclusion Criteria:

Order Number	Criteria
1	Subject Exclusion 1. Age < 18 years old or > 89 years old 2. Currently presenting with psychosis as determined by mental health consultant 3. Have a history of Cognitive disorder that would impair understanding of consent 4. Have a personal/family history of Schizophrenia 5. Currently pregnant or nursing 6. Serious and unstable medical condition/problems 7. Inability to medically clear 8. Non-English Speakers 9. Civilian Humanitarians 10. Have previously enrolled in this study

13.0 Recruitment and Consent

13.1 Please describe the recruitment process, including how subjects will be identified and selected for the study.

Subject Recruiting Methods

The method for subject recruitment is demonstrated in Figure 1. Explicitly they are as follows:

1. Patient Identification/Pre-screening
    1. Clinician will subjectively identify patients who present to the ED that express SI
    2. Clinician or nurse reviews EMR for documented inclusion/exclusion criteria
    3. Clinician will medically clear patient
2. Screening: The mental health liaison interviews patient, and along with the on-call mental health provider, determines whether or not patient requires inpatient psychiatric hospitalization.

3. Screen positive: Eligible patients, who are being hospitalized on inpatient psychiatry, are approached for consent. If intoxicated on presentation, they are approached when clinically sober.
4. Consent is obtained:
    1. Patient will complete BSSI & MADRS-S
    2. Treatment is administered per protocol
    3. Vitals and ADR are monitored
5. Potential medication contraindications will be indentified by treating physician, and a pharmacy consult will be obtained at the physician's discretion

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13.2 Compensation for Participation:

Subjects enrolled in the study will not be compensated monetarily.

13.3 Please describe the pre-screening process. If no pre-screening, enter Not Applicable in the text editor

All procedures in the management of the acutely suicidal patient will be in accordance with the standard of care, which includes a focused history and physical by an Emergency Medicine physician. Figure 1 demonstrates the flow of investigational procedures. The EM provider shall medically screen the patient and include appropriate ancillary studies. For example, if a patient is altered, intoxicated, sick-appearing, or exhibiting a clinical toxidrome, standard labs, EKG, or imaging will be ordered per standard of care. All female patients will have a urine HCG documented. Then, screening for admission to the psychiatric department will be done by the mental health liaison. This standard procedure will serve secondarily as the pre-screening method for this investigation. This will minimize duplication of work.

13.4 Consent Process: Revised Common Rule, Section 219.116: General requirements for informed consent, whether written or oral, are set forth in this paragraph and apply to consent obtained in accordance with the requirements set forth in paragraphs (b) through (d) of this section. Broad consent may be obtained in lieu of informed consent obtained in accordance with paragraphs (b) and (c) of this section only with respect to the storage, maintenance, and secondary research uses of identifiable private information and identifiable biospecimens.

Are you requesting a waiver or alteration of informed consent?

○ Yes ◉ No

Please explain the consent process:

Informed Consent Procedures
Research team members will review study procedures, potential risks and benefits of the study. Informed consent procedures will be conducted in private offices or exam rooms located in the ED. In accordance to 32 CRF 219, under no circumstances will the supervisors or commanding officers to the potential subject allowed to be present during the consent process. This is to ensure the avoidance of undue influence or coercion that may stem from the nature of the superior-subordinate relationship.

The patient will be approached for informed consent in accordance to with 21 CRF 50. They will be provided with a written document that embodies the elements of the informed consent. The consent will be presented orally to the subject with a witness. Once presented the subject will be given a reasonable time to review the contents and inquire information. All questions will be answered by the investigator obtaining consent. If consent is granted, the subject and the investigator will sign the consent form. A copy of the informed consent document will be given to the subject, and the original will be retained by the study investigator. This consent form will not be tied to any medical or data records. Consent forms will be maintained in a research specific locked drawer located in an investigator's/coordinator's office and only accessible by study the primary investigator, associate investigators or coordinator. The locked consent will be check by the P.I. or A.I. weekly.

In accordance with North Carolina State Law, if subjects are unable to consent for themselves due to emergent situations or impaired status, a LAR will be approached for consent. In the context of this study, subjects in these circumstances will be excluded from recruitment. If they are clinically intoxicated, consent will not be sought until they are clinically sober. Decisionally impaired subjects will not be approached for consent.

Vulnerable Populations

Due to the fact investigations take place in the ED, vulnerable populations that will recruited are persons in an emergency situation presents with situational cognitive vulnerabilities. Protections for this process have been put in place during the selection, and informed consent process. Furthermore, the selection of an interdepartmental research monitor will ensure the utmost care of this vulnerable population.

Under the Common Rule, DoDI 3216.02 military members are not considered a vulnerable population. However, due to the nature of hierarchical social structure they are more susceptible than the general population. Protections for this population will be in place during the consent process, and have been added to the consent verbiage.

13.5 DoDI 3216.02 requires an ombudsman to be present during recruitment briefings when research involves greater than minimal risk and recruitment of Service members occurs in a group setting. If applicable, you may nominate an individual to serve as the ombudsman.

- (•) N/A
- ( ) Propose ombudsman

13.6 Withdrawal from Study Participation:

Explain the process for withdrawal and specify whether or not the subjects will be given the opportunity to withdraw their data their data/specimens in the event they wish to withdraw from the study

Per Informed Consent Form:

"If you choose to participate, you are free to ask questions or withdraw from the project at any time without prejudice to your future care. Any new significant findings developed during the course of the research, which may affect your willingness to participate further, will be explained to you. Please notify Dr. Christine DeForest at 910-450-4840, Catherine Christian at **catherine.c.christian2.ctr@mail.mil** or Andrea Brzuska at 910-449-1141 to ensure an orderly termination process.

If you withdraw, you will no longer receive study drugs or treatments that are part of the study, unless these are also part of your normal drugs or treatments. Your withdrawal will involve no loss of benefits to which you are otherwise entitled. If you withdraw from this study, your data will be included in the data analysis for this project."

14.0 Risks and Benefits

14.1 Risks of Harm:

Identify all research-related risks of harm to which the subject will be exposed for each research procedure or intervention as a result of participation in this study. Consider the risks of breach of confidentiality, psychological, legal, social, and economic risks as well as physical risks. Do not describe risks from standard care procedures; only describe risks from procedures done for research purposes

List and Document Risks

The overall risk of an adverse event while using ketamine is very low, and easily manageable. Low dose IV ketamine can cause:

1. Transient Psychedelic effects – disturbances in visual and auditory perception, mood, body image, and time.
2. Hemodynamic changes – increase in blood pressure and heart rate

3. Psychotomimetic effects – mimicking the symptoms of psychosis, including delusions and delerium
4. Narcosis
5. Hypersalivation
6. Nausea and vomiting
7. Anxiety and Paranoia
    - Respiratory depression, apnea, laryngospasm, hypotension, bradycardia, myocardial infarction, central diabetes insipidus, anaphylaxis, increased intraocular pressure, increased intracranial pressure, porphyria and death.

(2) Justification of Risks

Ketamine holds a high degree of safety. In a review that describes over 70,000 patients only a single cardiorespiratory event of lasting significance was reported. Fully dissociative patients maintain their pharyngeal reflexes.[66]

Risk	Justification & Mitigation
Transient Psychedelic effects are disturbances in visual and auditory perception, mood, body image, and time. Patient may experience feelings of floating, conscious dreams, or hallucinations.[35] These effects occur between 50 and 200 ng/ml with more severe effects at higher doses. [34]	Dissociative symptoms are transient and will peak at 40 minutes and resolve within 120 minutes. [26] To mitigate psychiatric discomfort, **pre-induction coaching** will be provided. This is where the patient will be informed that they may have vivid dreams. [66] Signs of psychiatric discomfort will be managed with titratable sedatives (eg, midazolam) on an as needed basis.
Hemodynamic changes are extremely rare with ketamine use, especially with such a slow infusion.	Will be monitored hourly. Mild increases in heart rate can be mitigated by sympatholytic agents. Treatment will be stopped if pulse or systolic blood pressure increases > 25% of baseline, respiratory rate is sustained at < 7, or if severe psychomimetic effects or agitation present.
Psychotomimetic effects[33]	Can be mitigated through slow infusion or concomitant use of benzodiazepines if needed clinically.[24]
Narcosis (absence of verbal response) [33] at 0.5 mg/kg. This phenomenon is more likely with a quicker infusion.	This will be lessened or negated by mixing the dosage of medication in 100cc of NS and infusing slowly over 40 minutes.
Hypersalivation. Less likely at this concentration and with slow infusion.	This side effect can be addressed with concomitant use of glycopyrrolate if clinically indicated. [24]
Nausea and **vomiting**. Less likely at this concentration and with slow infusion. Generally, occur after emergence from dissociative state. [66]	This side effect can be addressed with use of ondansetron if clinically indicated. [68]
Psychopathological symptoms[65] such as difficulties in abstract thinking, lack of spontaneity, and decrease flow of conversation. This phenomenon is more likely with a quicker infusion.	This will be lessened or negated by mixing the dosage of medication in 100cc of Normal Saline and infusing slowly over 40 minutes.
Anxiety and Paranoia[65] can present at 500 ng/ml. This phenomenon is more likely with a quicker infusion.	This side effect can be addressed with use of a benzodiazepine if clinically indicated.

Acute Delirium can present at high doses or too fast administration of low doses (5 to 10 mg) [65]	This will be mitigated by the low dosage used in this investigation coupled with the slower infusion rate of 40 minutes and can be treated with a benzodiazepine if clinically indicated.
Transient respiratory depression & Apnea**.** Extremely Rare occurrence may occur with rapid delivery or concomitant use of midazolam.[66] Other **extremely rare**, serious adverse events have been reported: • laryngospasm, hypotension, bradycardia, myocardial infarction, and death.	This will be mitigated through appropriate weight-based dosing, slow infusion, careful monitoring of those on concomitant midazolam.[66] Mitigation of these events will be through continuous hemodynamic monitoring including pulse oximetry.[66]

- For full list of possible adverse drug reactions see Patient Drug Handout in Appendix D.

14.2 Measures to Minimize Risks of Harm (Precautions, safeguards):

For each research procedure or intervention, describe all measures to minimize and/or eliminate risk of harms to subjects and study personnel

Minimization of Risks

In general, slow infusion of low-dose ketamine has been shown to significantly reduce reporting of moderate to greater side effects, specifically hallucination s and feelings of unreality.67 We will be excluding those patients most vulnerable to adverse events, such as those with a history of psychosis, schizophrenia, or schizoaffective disorder. Because Ketamine is pregnancy category B, they will be excluded from the study. Patients will also be excluded medically at the discretion of the treating physician or if they are being involuntarily admitted. Vital sign monitoring every 5 minutes will ensure adverse drug reactions are addressed promptly.

Although the dose used should not induce emergence reaction, it should be noted that transition to conscious perception can be terrifying, and severe emergence reaction can be a traumatic experience. This effect will be inherently mitigated through the low dosage used. Furthermore, pre-induction coaching, slow infusion, and PRN administration of midazolam strategy will be used to mitigate this potential adverse side effect.66

14.3 Confidentiality Protections (for research records, data and/or specimens):

Describe in detail the plan to maintain confidentiality of the research data, specimens, and records throughout the study and at its conclusion (e.g., destruction, long term storage, or banking). Explain the plan for securing the data (e.g., use of passwords, encryption, secure servers, firewalls, and other appropriate methods). If data will be shared electronically with other team members/collaborators outside the institution, describe the method of transmission and safeguards to maintain confidentiality. Explain whether this study may collect information that State or Federal law requires to be reported to other officials or ethically requires action, e.g., child or spouse abuse

Protection and Security of Data and Identifying Information

1. Handling of paper questionnaires will be as follows:
    1. Questionnaires will be placed in trial mailbox.
    2. They will be kept in a locked box in a locked office, until they can be scanned into a secure digital folder.

2. Digital protection:
    1. Data will be stored in accordance to Navy HRPO policy and data storage policies
    2. Password protection: Each patient will be assigned a subject identifier during randomization. This file will be password protected.
        1. The data will remain on a study team member's computer which is only accessible with a CAC card.
    3. De-Identification: Only subject identifiers will be used in psychometric testing. Additionally, as shown in Figure 2, the subject identifier will be the only means to connect to various data related to the subject. The Subject identifier will be stored separate from all de-identified information.
    4. Separation of data: Data collection sheets will be separated into different files, as shown in Table 3.

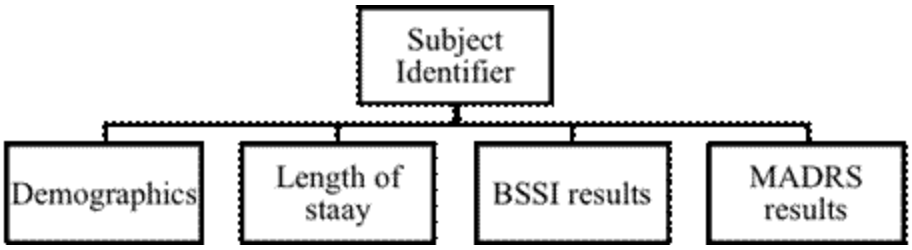

Figure 2: Subject Identifier connection to other data sheets for a participant

Table 3: Security Management breakdown of Data Collection Sheets

Spreadsheet	Contents	Who has access?	Security
Subject Identifier key	Subject identifier code & Patient name	NMCCL Investigators	Password protected
Demographics	Email, gender, DOB, age, number of previous attempted suicide, history of self-harm, psychiatric history, recent antidepressant use, current psychotropic medication, classification (military/civilian)	Only Investigators	Separate file
LOS	Time of admission & transfer	Only Investigators	Separate file
BSSI	BSSI results	Only Investigators	Separate file
MADRS	MADRS results	Only Investigators	Separate File

(6) Disposition of Data and Identifying Information at End of Project

Specified data will be stored digitally in accordance to Navy regulation. All other documents will be disposed per Navy Instruction at the conclusion of the storage period. In accordance to DHHS protection of human subject's regulation, IRB activities and records will be maintained in digitally secure location for at least three years (45 CFR 46.115(b)). In accordance to HIPAA requirements, data that fall under this regulation will be stored for at least six years.

14.4 Potential Benefits:

Describe any real and potential benefits of the research to the subject and any potential benefits to a specific community or society

If the individuals in the research are considered experimental subjects (per 10 USC 980), and they cannot provide their own consent, the protocol must describe the intent to directly benefit all subjects

Benefits

1. It is possible that subjects may not receive any benefit from participation especially those in the placebo arm. However, it is likely they will experience a small degree of benefit from the placebo effect.

2. Subjects in the experimental arm have the potential to experience a decrease in SI, and LOS in the ED. Thus, improving their quality of care. The experimental protocol may have a positive impact on their mental state post discharge. Thereby decreasing their risk for repeat attempts.
3. Subjects enrolled in the study will not be compensated monetarily.

14.5 Privacy for Subjects:

Describe the measures to protect subject's privacy during recruitment, the consent process, and all research activities, etc.

Informed consent procedures will be conducted in private offices or exam rooms located in the ED. In accordance to 32 CRF 219, under no circumstances will the supervisors or commanding officers to the potential subject allowed to be present during the consent process. This is to ensure the avoidance of undue influence or coercion that may stem from the nature of the superior-subordinate relationship.

A copy of the informed consent document will be given to the subject, and the original will be retained by the study investigator. This consent form will not be tied to any medical or data records. Consent forms will be maintained in a research specific locked drawer located in an investigator's/coordinator's office and only accessible by the study primary investigator, associate investigators, or coordinator. The locked consent will be check by the P.I. or A.I. weekly.

14.6 Incidental or Unexpected Findings:

Describe the plan to address incidental findings and unexpected findings about individuals from screening to the end of the subject's participation in the research. In cases where the subject could possibly benefit medically or otherwise from the information, state whether or not the results of screening, research participation, research tests, etc., will be shared with subjects or their primary care provider. State whether the researcher is obligated or mandated to report results to appropriate military or civilian authorities and explain the potential impact on the subject

In the case of incidental findings, it will be at the discretion of the PI whether or not to inform the subjects of these findings.

15.0 Study Monitoring

15.1 Your study requires either Data and Safety Monitoring Plan (DSMP) or a Data and Safety Monitoring Board (DSMB).

- ○ DSMP
- ○ DSMB
- ○ Both
- ◉ Not Applicable

16.0 Reportable Events

16.1 Reportable Events: Consult with the research office at your institution to ensure requirements are met. Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event.

Consult with the research office at your institution to ensure requirements are met

• Describe plans for reporting expected adverse events. Identify what the expected adverse events will be for this study, describe the likelihood (frequency, severity, reversibility, short-term management and any long-term implications of each expected event)

• Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the research protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event

ADVERSE EVENT MANAGEMENT AND REPORTING
Unanticipated problems involving risk to subject or others, serious and unexpected adverse experiences related to participation in the study and all subject deaths will be promptly reported in accordance with the requirements of the Naval Medical Center Camp Lejeune Institutional Review Board. The local site PI and/or overall study PI will report all serious adverse events (SAE) occurring among enrolled subjects to the NMCCL IRB within 24 hours of the discovery of the adverse event. The PI will submit an internal adverse event report memorandum to the IRB. Unexpected (but not serious) adverse events occurring among enrolled subjects which, in the opinion of the local site PI or overall study PI, are possibly related to participation in the protocol, will be reported by the local site PI and/or overall study PI within 24 hours to the IRB using this same procedure. A summary of all adverse events will be submitted along with the annual continuing review report.

Serious adverse events will be addressed through standard emergency resuscitative care (Table 5) will be rendered. The IRB will be notified within 24 hours of any case of serious adverse events.

Table 5: Rapid overview for the management of ketamine intoxication[69]

Clinical presentation
Impaired consciousness is the most common presentation, although ketamine intoxication may cause a range of central neurologic symptoms, from mild agitation to hallucinations; mild tachycardia and hypertension often occur
Massive overdose can cause coma or apnea
Laryngospasm and heavy salivation may infrequently occur during intravenous use, even with standard doses; laryngospasm is rare but occurs most often in infants
Vertical or rotatory nystagmus may occur
Diagnostic testing
Diagnosis of ketamine intoxication is based on history and clinical evidence; no readily available definitive laboratory test exists
Obtain fingerstick glucose, acetaminophen and salicylate concentrations, electrocardiogram, and pregnancy test in women of childbearing age
Management
Secure airway, breathing, and circulation
Laryngospasm and respiratory depression
Generally, resolve with noninvasive support (e.g., bag-mask ventilation; oxygen); endotracheal intubation is rarely required
Salivation that compromises respirations or interferes with procedures
Treat with **glycopyrrolate** (5 mcg/kg, may be repeated once after five minutes)
Psychomotor agitation
Treat with **benzodiazepines** (e.g., intravenous doses of **diazepam** 0.1 mg/kg or in adults 5 to 10 mg, or **lorazepam** 0.05 mg/kg or in adults 1 to 2 mg) until the desired level of sedation is achieved
Butyrophenones (e.g., haloperidol, droperidol) and other antipsychotic agents **should not be used** to treat agitation
Disposition

Patients with uncomplicated ketamine toxicity may be observed and discharged when symptoms have resolved

17.0 Equipment/non-FDA Regulated Devices

17.1 Does the study involve the use of any unique non-medical devices/equipment?

○ Yes ◉ No

18.0 FDA-Regulated Products

18.1 Will any drugs, dietary supplements, biologics, or devices be utilized in this study?

☑ Drugs
☐ Dietary Supplements
☐ Biologics
☐ Devices
☐ N/A

18.2 Drugs, Dietary Supplements and Biologics/Vaccines details:

☑ Are drug(s) in this research being used in accordance to the approved labeling?
☑ Are drug(s) in this research being used in a manner other than its approved labeling?

Enter Dietary Supplements and Biologics/Vaccines in the Drug Information table. Complete all relevant fields in the table ("Protocol Drug Details" screen). If the question is not relevant, leave the question blank and/or do not change the default selection.

View Details	Drug Name	FDA Approved	A new drug or a new use of approved drug:	IND Number
⊟	**Trade Drug Name:** ketamine **Generic Drug Name:** **Investigational Drug Name:**	Yes	No	

Trade Drug Name:	ketamine
Generic Drug Name:	
Investigational Drug Name:	
Identify the name of the manufacturer or source of investigational drug/biologic:	Mylar Institutional LLC, Rockford, IL
Is the drug supplied at no cost?	Yes
Is the Drug FDA Approved:	Yes
Is this a new drug or a new use of an already approved drug	No
Is an IND necessary	No
IND Number	

Who holds the IND:	N/A
IND details:	
If FDA Approved and an IND is not required, Please provide a rationale for exemption:	I. It is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug; RESPONSE: It will not be reported to the FDA for a new indication or to change labeling ii.it is not intended to support a significant change in the advertising for the product; RESPONSE: we do not intend to change the advertising for the product. iii.it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product; RESPONSE: it will not significantly affect dosing or risks of using medication iv.it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively]; RESPONSE: it has been reviewed by an IRB and informed consent will be obtained v.it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and RESPONSE: will be conducted in compliance with 21 CFR 312.7 vi.it does not intend to invoke 21 CFR 50.24. RESPONSE: does not intend to invoke 21 CFR 50.24
Are you currently using this IND in another research project?	No
If yes, list the IRB Number(s):	
Dose Range:	0.5mg/kg in 100 cc normal saline
Frequency:	single IV infusion over 40 minutes
Route of administration:	IV
Will the investigational pharmacy be dispensing?	No
If the source is not a FDA licensed facility, provide details regarding the purity, quality, stability and sterility of the investigational drug/biologic:	NMCCL pharmacy
Identify who will be preparing the investigational drug/biologic for administration and describe in detail how it will be prepared:	Pharmacy staff
Indication(s) under Investigation:	suicidal ideation
Where will the drug be stored	NMCCL pharmacy
Drug Storage Restrictions (including temperature, etc.):	Stored according to NMCCL pharmacy standards
Administration Instructions:	standard administration
Possible Untoward Effects, Their Symptoms & Treatment:	see protocol sections regarding risks
Potential or Actual Antidotes for Excessive or Adverse Drug Effect:	see protocol for adverse reaction treatment
Contraindications and Interactions, If Known:	see protocol for contraindications
Investigators Authorized to Prescribe:	Clinicians with ED priveledges

18.4 Reporting Requirements for FDA-regulated research under IND and IDE:

Describe the process for complying with FDA regulatory requirements for adverse event reporting and adverse device effects reporting to the sponsor

18.5 Sponsor (organization/institution/company):

☑ N/A

If applicable, provide sponsor contact information:

19.0 Research Registration Requirements

19.1 ClinicalTrials.gov Registration:

○ Registration is not required
○ Registration pending
◉ Registration complete

"NCT" number:

NCT04260607

19.2 Defense Technical Information Center Registration (Optional):

◉ Registration is not required
○ Registration pending
○ Registration complete

20.0 References and Glossary

20.1 References:

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20.2 Abbreviations and Acronyms: