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II. TITLE:

CAP-Ketamine for Antidepressant-Resistant PTSD (NCT02655692)

III. PURPOSE:

The purpose of the proposed research is to test the safety and efficacy of repeated doses of ketamine as compared to placebo, in reducing symptoms of Posttraumatic Stress Disorder (PTSD) in an active duty military and Veteran population.

PTSD is the psychiatric disorder that can be most directly attributed to participation in combat. Thus the Department of Veterans Affairs and Department of Defense have a unique responsibility to identify and implement effective treatments for military personnel and Veterans suffering from PTSD. Despite the existence of two FDA-approved serotonergic (SSRI) antidepressants for the treatment of PTSD, these medications take 1-3 months to separate from placebo in multisite clinical trials[1-4] and often do not yield complete symptom remission. Additionally, a widely advocated treatment strategy for SSRI-resistant PTSD symptoms, utilizing the addition of risperidone, did not show efficacy in one definitive trial.[5] Therefore, <u>there is a tremendous need to identify more effective and more rapidly acting pharmacotherapies for PTSD that work through novel neural mechanisms</u>. Here we propose to test a medication that may meet these criteria. More than 15 years ago, we identified the rapid-onset of antidepressant effects of the *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist, ketamine.[6] By 24 hours following a single dose, antidepressant response rates range between 50%-90%.[7] The benefits of single doses have been extended by up to 6 doses in randomized trials and for up to 18 months of repeated dosing in published and unpublished case series. A single study has attempted to extend this work to PTSD. This study, conducted in 41 civilians at the Mount Sinai School of Medicine, found that a single dose of ketamine rapidly reduced PTSD symptoms compared to midazolam, even in patients who did not have comorbid depression.[8] Therefore a definitive clinical trial is now needed to answer the following questions: (1) do the benefits of ketamine extend to Veterans and active duty military populations; (2) may these benefits be safely extended through repeated dosing; (3) does ketamine have dose-related effects in PTSD; and, (4) what is the durability of benefit among responders to short-term treatment?

Primary specific aim: *To test the dose-related effects of ketamine on PTSD symptoms in the Veteran and active duty military populations*. In this 2-site study, approximately 198 eligible Veterans and active duty personnel who meet criteria for PTSD and the additional inclusion and exclusion criteria (detailed in Section III-A) will be randomized to one of three treatment arms (placebo, ketamine 0.2 mg/kg, ketamine 0.5 mg/kg). Participants will receive the study drug or placebo via intravenous infusion twice per week for 4 weeks. The primary outcome measure will be the PTSD Checklist (PCL-5). Data will be stratified by site (Texas vs. Connecticut) and by the presence of comorbid mild-to-moderate alcohol dependence. A random effects/mixed model will be applied to the data. The study is powered based on the effect size of ketamine in the Mount Sinai study to detect a significant interaction of ketamine dose and time during this trial.

Secondary specific aims:

1. Safety of repeated ketamine exposure: We will evaluate the safety of ketamine exposure in the following ways: (1) induction and persistence of psychotic and dissociative symptoms will be evaluated during ketamine infusion, prior to discharge at each ketamine test day, and at two weeks and one month following the last ketamine infusion; (2) breath alcohol levels will be evaluated prior to randomization, throughout the trial, and for 4 weeks following the last ketamine exposure; (3) medical and psychiatric adverse events and serious adverse events will be recorded following FDA, VA Cooperative Studies Program, and Consortium for the Alleviation of PTSD (CAP) guidelines.

2. Durability of benefit: Following completion of the randomized testing, psychometric ratings (PCL-5 and other outcome measures) and safety assessments will be obtained on a weekly basis for 4 weeks to qualitatively and quantitatively characterize (random effects model covarying for end-of-treatment severity) the dose-related durability of benefit in responders to the randomized treatment.

3. Clinical significance of PCL changes: Following the lead of the VA Cooperative studies, we will use the PCL-5 as the primary outcome variable due to its sensitivity to pharmacotherapy effects, lower respondent burden, and to reduced site-specific rater effects relative to the Clinician-Administered PTSD Scale (CAPS). The CAPS-5 (using the DSM-5 criteria for the diagnosis of PTSD) will be obtained at baseline, at the end of randomized treatment, and at 4-week follow-up. Global/functional impact of treatment will be evaluated with the Clinical Global Impression Scale (CGI), and the Veterans Rand 12-item Health Survey (VR-12).

4. Integrity of the blind: At the end of the randomized treatment, participants will be asked to name the study arm that they believe they were assigned to and to identify their level of confidence in their designation.

II. BACKGROUND

There is a tremendous need to test novel pharmacotherapeutic approaches to PTSD. PTSD is a leading cause of disability amongst trauma-exposed military and civilians alike. The National Comorbidity Survey Replication (NCS-R) estimates the lifetime prevalence of PTSD among adult Americans to be 6.8%.[9] The US Department of Veteran Affairs estimates that PTSD afflicts 11% of Veterans of the war in Afghanistan and 20% of Iraqi war Veterans. While antidepressant medications are currently available, the efficacy of these medications is limited.[10-12] Currently, only two medications, both selective serotonin reuptake inhibitors (SSRIs), have FDA approval for the treatment of PTSD. These medications take weeks to months to reach full clinical effects. In civilian treatment seeking populations, fewer than half of the patients achieve full remission

on SSRIs. The rates of non-response or partial response to these medications among combat-exposed military, particularly those with chronic PTSD, are comparable or worse to those of the civilian patient population.[13,14] Currently, there are no pharmacotherapies for SSRI-resistant PTSD symptoms that have efficacy supported by a definitive, multicenter, placebo-controlled trial. For example, a second-generation antipsychotic medication did not show efficacy for antidepressant-resistant PTSD symptoms in our recent VA multicenter trial.[5] Hence, there is an urgent need for a novel class of antidepressants that can offer (1) rapid acting effects and (2) efficacy in patients not achieving adequate benefit from existing medications. Over the last decade, accumulating evidence has shown that low dose of ketamine, a *N*-methyl-D-aspartate receptor (NMDAR) antagonist, may possess these properties.

The NMDA receptor antagonist, ketamine, is a rapid-acting antidepressant and is effective in treatment-resistant depression. Seventeen years ago, we first reported the antidepressant effects of ketamine at the 1997 ACNP meeting. Published reports from our group, NIMH, Mount Sinai, and now several other groups indicate that ketamine produces reductions in antidepressant-resistant depression symptoms within 4 hours and full clinical response in 50-90% of patients within 24 hours.[6,15] Ketamine is effective in reducing all aspects of depression, including suicidal ideation.[16,17] This antidepressant effect is shared by different types of NMDA antagonists in animals and humans.[18-20] Although ketamine is a short-acting medication, antidepressant response to a single ketamine dose may last 2 weeks or more and the duration of benefit may be extended by repeated dosing.[21] Repeated ketamine administration has been well tolerated and has sustained the antidepressant effects for more than 2 weeks.[21] Case study series suggest that with 50 or more ketamine infusions, clinical responses are sustained without the emergence of adverse events.[22,23]

Preliminary evidence supports the utility and safety of ketamine in treating PTSD symptoms. A recent case report described a young Veteran with highly treatment-resistant PTSD. The patient showed rapid improvement following a single infusion of subanesthetic dose of ketamine treatment with 56% reduction in his PTSD symptoms. The treatment response was maintained for 15 days. Ketamine was well tolerated and no adverse effects were reported.[24] Another case series reported marked reduction in flashbacks in three women with PTSD treated with ifenprodil – an NMDA receptor antagonist that selectively binds to the GluN2B subunit.[25] More recently, Zeng and colleagues reviewed the safety of subanesthetic doses of ketamine in 10 subjects with PTSD and 20 subjects with a history of sexual or physical abuse who were treated with ketamine for comorbid treatment-resistant unipolar or bipolar depression. They found that ketamine was well tolerated with no evidence of worsening in PTSD symptoms.[26] Finally, data from a recent study conducted at Mount Sinai by Feder and colleagues provided pilot evidence supporting the utility and safety of ketamine in treating PTSD symptoms in a largely civilian population.[27] This pilot study randomized 41 PTSD patients to a single infusion of ketamine (0.5 mg/kg infused over 40 min; n = 22) or midazolam (n = 19) in a double-blind crossover design. Compared to midazolam, ketamine showed a significant improvement in PTSD symptoms 24 hours post infusion [mean difference = 12.7, p = 0.017]. Similar to depression studies, dissociative symptoms occurred during infusion, peaked at 40 min, were well tolerated, and completely resolved within 80 minutes following ketamine administration. Only one subject decided to exit the study because he felt uncomfortable during infusion. Physical adverse effects were transient, and comparable to those found in ketamine studies in healthy and depressed subjects.[27]

III. SIGNIFICANCE:

Contribution of the current trial for the development of future therapeutics: The first step would be to prove that ketamine was an effective treatment for PTSD. To date, only one randomized

study evaluating the effectiveness of a single infusion of ketamine (one dose, 0.5 mg/kg) has been studied in 22 PTSD patients in comparison to 19 PTSD patients who were administered midazolam at Mount Sinai.[27] The present revised study builds upon the pilot data from the Mount Sinai study to address many of the limitations of its study design: 1) *Sample size* – The proposed study is much larger and likely to yield definitive results, 2) *Dose* – The proposed study would compare two doses of ketamine (0.2 mg/kg, 0.5 mg/kg), 3) *Inactive comparator* – This study would incorporate placebo as a reference for evaluating ketamine effect, 4) *Study population* – The prior study was conducted in a civilian population while the proposed study would recruit active duty personnel, Veterans who served in combat following 9/11, and other Veterans, 5) *Outcome measure* – the prior study employed the Impact of Events Scale as the primary outcome measure, while the proposed study would employ the PTSD Checklist-5 (which yields score highly correlated with CAPS-5 but with reduced respondent burden), and 6) *Number of ketamine infusions* – We propose 8 ketamine infusions over 4 weeks followed by a 4-week follow-up making this trial the length of many standard PTSD studies. Thus this study is a critical bridge between the initial observation in PTSD and the development of NMDA receptor antagonist administration as a treatment for PTSD. A significant result ($p \leq 0.05$, two-tailed) for our primary analysis would serve as the basis for a "go decision" and continued research and development of ketamine as a viable treatment alternative for PTSD. It would also justify the exploration of more highly experimental subtypes and selective NMDA receptor antagonists (ifenprodil, Glyx-13, AZD-6765, CP101, 606, etc.) for the treatment of PTSD.

IV. RESEARCH PLAN:

This study is being conducted as part of the Consortium To Alleviate PTSD (CAP) and is proposed as a 2-site, 3-arm randomized, double-blind, controlled clinical trial to test the safety and efficacy of repeated doses of ketamine as compared to placebo, in reducing symptoms of Posttraumatic Stress Disorder (PTSD) in an active duty military and Veteran population.

A. Subjects:

Across both sites, we anticipate recruiting, consenting, and screening approximately 240 male and female Veteran and active duty military subjects (~120/site), between the ages of 18-70 years, in order to meet the target enrollment goals. In order to account for subject drop outs and the potential need to discontinue subjects before study completion (see below for discontinuation criteria) and retain a sample of ~159 subjects completing the double-blind treatment phase (~53 per treatment group), approximately 198 eligible subjects (~66 in each group) who meet criteria for PTSD as determined by the Clinician Administered PTSD Scale (CAPS-5) and the study inclusion criteria outlined below, will be randomized.

At the West Haven VA, we intend to randomize approximately 99 Veteran and active duty military personnel. In order to account for subject dropouts and the potential need to discontinue subjects before study completion (see below for discontinuation criteria) and retain a sample of at least ~80 subjects completing the double-blind treatment phase, approximately 120 eligible subjects (see below for eligibility criteria), will be randomized into the study.

B. Inclusion and Exclusion Criteria:

Inclusion Criteria:

1. Male or female Veterans and active duty military personnel between the ages of 18-75 years seeking treatment for PTSD.
2. Diagnosis of PTSD with a score of 23 or higher (i.e. severe PTSD) on the Clinician-Administered PTSD Scale (CAPS-5) at screening.

3. Treatment resistance to at least one adequate trial of an antidepressant as determined by the Massachusetts General Hospital Antidepressant Treatment History Questionnaire (MGH-ATRQ).
4. Subjects on prescribed nicotine replacement therapy (i.e. patch/lozenge) may enter the study and continue the prescribed nicotine treatment for the duration of their participation. Should the participant plan to use their nicotine replacement therapy during infusion visits, it is asked that they bring in the original packaging with the prescription label on it.
5. Subjects on FDA-approved antidepressant, trazodone, atypical neuroleptic, prazosin, or clonidine may enter the study if they have been on an overall stable treatment, as determined by the study clinician, for at least 4 weeks prior to randomization. Following randomization, changes to doses may be allowable at the investigator's discretion.
6. Subjects in PTSD-focused psychotherapy may be enrolled if they have been in therapy for 6 weeks prior to randomization.
7. Able to provide written informed consent.
8. Able to read and write English.

Exclusion Criteria:

1. Subjects with a diagnostic history of schizophrenia or schizoaffective disorder as confirmed by the Mini-International Neuropsychiatric Interview (MINI) 7.0 for DSM-V.
2. Subjects with a history of antidepressant-induced hypomania or mania.
3. Subjects currently exhibiting psychotic features or meeting criteria for current manic, hypomanic, or mixed episode as confirmed by the MINI 7.0 for DSM-5.
4. Current, ongoing serious suicidal risk as assessed by evaluating investigator.
5. Moderate severity or greater Substance Use Disorder (excepting Alcohol Use Disorder) during the 3 months prior to randomization, as determined by the MINI 7.0 for DSM-5. Alcohol Use Disorder may be allowed based on the judgment of study physician/APRN/clinician that patients can remain sober for all study visits.
6. Subjects on a prohibited medication (see Table 1). Patients will not be taken off medication for the purpose of this study.
7. Any history or signs of serious medical or neurological illness. A subject with a clinical abnormality may be included only if the study clinician considers the abnormality will not introduce additional risk factors and will not interfere with the study procedure.
8. History of traumatic brain injury (TBI) with loss of consciousness for more than 24 hours or posttraumatic amnesia for more than 7 days may be considered if the trauma occurred more than 1 year ago, and no more than minimal symptoms have persisted over the past year.
9. Breathalyzer showing an alcohol level > 0% at screening, or at the discretion of the investigator, prior to any study drug infusion.
10. Any history indicating dementia or mental retardation as determined by psychiatric interview.
11. Known sensitivity to ketamine as determined by the study clinician.
12. At screening, resting blood pressure (sitting or supine) lower than 90/60 or higher than 150/90, or resting heart rate lower than 45/min or higher than 100/min.
13. Females will be excluded if they are pregnant (i.e. positive pregnancy test at screening or prior to any study drug infusion); breastfeeding; or do not agree to utilize a medically accepted birth control method (e.g. oral, injectable, or implant birth control, condom, diaphragm with spermicide, intrauterine device, tubal ligation, abstinence, or partner with vasectomy). Women who are surgically sterile or have been post-menopausal for at least 1 year, will not be excluded.

Table 1. Concomitant Treatments that are prohibited

Use category	Type of medication	Details
Prohibited	MAOIs	4-weeks off medication prior to randomization is required.
	Memantine	4-weeks off medication prior to randomization is required.
	Long Acting Benzodiazepines: Chlordiazepoxide, Diazepam, Flurazepam	2-weeks off medication prior to randomization is required.

Notes: As above, individuals who have used any of the prohibited medications within the "weeks off" time period will not be eligible for the study. Use of sedatives, hypnotics, benzodiazepines, sedating antihistamines or other psychotropic medications are not permitted within 8 hours of treatment sessions; except – at the discretion of the investigator – for medications that will result in discontinuation/withdrawal symptoms or that may alter the risk benefit ratio.

C. Privacy:

All reports generated from the data obtained through this study will protect the confidentiality of the subjects who participate in this study. In case of a medical emergency, the medication group blinding can be broken by the principal investigator or a designated covering staff member, in order to supply information required for emergency medical care of research subjects. All subjects will be given a "wallet card" which identifies them as a study participant and lists the emergency contact numbers. If a subject shows clinical deterioration (e.g. suicidality, worsening PTSD symptoms), the principal investigator (or medical designee) will determine whether the subject can safely remain in the study or needs to be evaluated for a higher level of care

D. Selection:

Subject eligibility will first be determined via telephone screening and if records are available, by a preliminary medical record review. A waiver of HIPAA authorization and written informed consent will be obtained for a brief initial phone pre-screen and preliminary medical record review. The phone pre-screen and possible medical record review will be done to identify obvious study exclusions and prevent subjects from making unnecessary trip to the study site for the detailed screening process. All other study-related screening for inclusion and exclusion will only be collected following a face-to-face written informed consent process (described below). Following a face-to-face evaluation and discussion with the research team, an experienced study physician/advanced practice registered nurse (APRN) and/or co-investigator will determine suitability for enrollment and randomization.

E. *Recruitment & Consent*:

We will employ a multisite enrollment strategy to ensure the enrollment of a total of approximately 198 participants. Participating sites include the Clinical Neuroscience Division of the National Center for PTSD (NCPTSD) at West Haven, Connecticut VAMC, and the San Antonio Military Medical Center (SAMMC) in San Antonio Texas with whom STRONG STAR has a

collaborative affiliation. In addition to recruiting efforts at the participating sites, we may also contact local colleges that house Veteran Service Centers to inform them of our research.

Subjects may also be recruited through word of mouth, clinician referral, referral through the National Center for PTSD's centralized screening protocol (IHR0010) or the National Center's Biomarkers Development for Mental Disorders protocol (CA0008), contact with community service groups and clinics. Additional recruitment may be conducted through flyers, public advertisements (e.g., print, newspaper, radio, bus, billboards, online postings (including Trialfacts/Rewards for Research online marketing and recruitment service), social media (e.g., Facebook, Twitter, Instagram), digital media (e.g., TV, online radio, podcasts) and news releases. Additionally, we will recruit from flyers, clinician referrals, and word of mouth at VAMCs, Vet Centers and CBOCs throughout New England (CT, RI, MA, VT, NH, ME) and the Tri-State Area (NJ-NY-CT). We intend to register our study on clinicaltrials.gov. We may also utilize the National Center for PTSD newsletter to advertise the study.

We plan to send letters from the study PI to potentially eligible Veterans and active duty military personnel; these letters will consist of a description of the study and a notification that they may receive a phone call from a research staff member within ten (10) days in order to give them additional information and assess interest. Up to three (3) attempts will be made to contact the Veteran before attempts stop. The letter will include contact information for relevant staff, and will clearly state the option to opt out of receiving any research calls by letting us know that they do not wish to be contacted. No phone calls will be made to Veterans that contact us to opt out. When feasible, these recruitment methods may be employed in areas encompassing New England (CT, RI, MA, VT, NH, ME) and the Tri-State Area (NJ-NY-CT). A list of Veterans will be retrieved from VINCI using a PTSD diagnosis as the primary criteria for inclusion.

VA Informatics and Computing Infrastructure (VINCI):
The VA Informatics and Computing Infrastructure (VINCI) is a major informatics initiative of the Department of Veterans Affairs (VA) that provides a secure, central analytic platform for performing research and supporting clinical operations activities. It is a partnership between the VA Office of Information Technology (OI&T) and the Veterans Health Administration Office of Research and Development (VHA ORD). VINCI includes a cluster of servers for securely hosting suites of databases integrated from select national VA data sources. VINCI servers for data, applications and virtual sessions are physically located at the VA Austin Information Technology Center (AITC), located in Austin, Texas. This secure enclave with 105 high-performance servers and 1.5 petabytes of high-speed data storage has multiple layers of security and disaster recovery to prevent data loss.

To ensure the protection of Veteran data, VINCI maintains compliance with the guidelines set forth by Veterans Health Administration (VHA) Handbook 1200.12, Use of Data and Data Repositories in VHA Research, and all other applicable VA and VHA policies and regulations. In addition, VINCI has undergone all security certification activities in support of obtaining an Authorization to Operate (ATO). Access to VINCI resources are approved in accordance with the requirements of National Data Systems (NDS), VHA Handbook 1200.12, Use of Data and Data Repositories in VHA Research, and all other applicable VA and VHA policies and regulations. All data transferred from VINCI is subject to audit for compliance.

VA-credentialed research or operations staff are granted access to study-specific data along with tools for analysis and reporting in the secure, virtual working environment through a certified VHA network computer within the VA. If not working within a VA or VHA hosted office environment containing VA network access, researchers may apply for and then access VINCI through an approved Virtual Private Network (VPN) and Remote Desktop application. The remote computing environment enables data analysis to be performed directly on VINCI servers, offering a number of advantages: uniform security standards for access; a common point of entry for all investigators who use the data; tools for analysis and reporting; tighter and more consistent control of data quality; and the ability to standardize and update terminology and format as technology and methodology improve.

Data Collection

VA provides care to Veterans at over 1,400 points of care. At the core of virtually all care processes is a broadly scoped and extensively used electronic health record system known as the Veterans Information System Technology Architecture (VistA). VistA provides a longitudinal view for patients receiving care nationwide including diagnoses, procedures, medications, labs, physiologic measurements, and text notes and reports. VA uses 130 VistA implementations to provide electronic health record services nationwide for just over 20 million Veterans historically. The aggregate content of these 130 VistA systems includes 2.3 billion documents (e.g., Progress Notes, Discharge Summaries, Reports) accumulating at a rate of 696,000 each day; 6.2 billion lab values (+1.5 million each day), 3.4 billion orders (+845,000 each day), and 1.7 billion medication administrations and prescription fills (+390,000 each day).

Data are aggregated from individual VistA systems to the VA Corporate Data Warehouse where it is modeled and prepared for use. Data published by the VHA Decision Support System (DSS), Inpatient and Outpatient Medical SAS (MedSAS), VA Health Economics Resource Center (HERC) cost data, Vital Status and VA-CMS linked data files maintained by VA Information Resource Center (VIReC), CDC National Death Index VA-linked data, and several other specialty data sets can be requested through VINCI. VA National Data Services and other data stewards regulate the right to use the data, but VINCI facilitates the process. When study requests are approved, project-specific data are extracted from source databases and placed in SQL tables accessible only to the research team and VINCI data managers.

Storage of Study Data

Study data will be kept in accordance with the Department of Veterans Affairs Record Control Schedule 10-1 (RCS 10-1). Storage and transfer of any Personally Identifiable Information (PII) or Protected Health Information (PHI) must be done in accordance with applicable VA and VHA policies and directives, state and federal regulations, and applicable statutes including the Health Insurance Portability and Accountability ACT (HIPAA). Unless explicitly requested and approved by data stewards, all sensitive patient data must remain on VINCI project servers and only aggregate data without PII / PHI may be transferred from VINCI. Any desired change in data storage location or transfer requires

amending the original data request with an updated of disposition of study data. The amendment must be approved by all data stewards before data may be transferred.

Violations of data policy or approved use of data will be subject to full penalty of law, which may include suspension of access privileges, reprimand, suspension from work, demotion, removal, and criminal and civil penalties.

Upon completion of the research project, the study principal investigator in conjunction with the VA Information Security Officer (ISO), and in accordance with VA policy, will ensure that, study data containing sensitive, confidential information will be returned to the VA, sanitized and removed from all servers, desktops, removable storage devices, etc.

Data Access
Only study team personnel explicitly authorized by data stewards will have access to project data. The study principal investigator has the responsibility for security of study. VINCI data managers and VA OI&T personnel not under the purview of the study principal investigator control the servers, network, processors, firewall and software in the VINCI environment, including access rights granted to study personnel.

When study personnel are no longer part of the research team, the study principal investigator will amend the data access request to terminate that person's access to all study data and notify the VA Information Security Officer of such action. No sensitive patient data may be shared with anyone who does not have a VA appointment. All study team personnel with access to sensitive patient data must stay current on required VA information security and privacy policy trainings.

Data Storage Location
Study data stored on VINCI servers is located at the Austin Information Technology Center, 1615 Woodward St., Austin, TX 78772-0001. The specific server where the data are stored within the VINCI environment will be chosen by VINCI personnel. The server name and location within the Austin Information Technology Center may be changed at any time at the discretion of VINCI personnel.

Specialized Software
All software used to access sensitive patient data, whether provided by VINCI, or developed by the study team, will run in virtual desktop sessions on VINCI servers within the Austin Information Technology Center.

Subjects will be identified by their response to advertisements and/or internal recruiting and referral. The subjects will be asked to call us if they are interested in participating in the research study. Study staff may contact patients referred by their providers, but research staff will not make cold calls. A waiver of HIPAA authorization and written informed consent will be requested for a phone screen and preliminary medical record review in advance of scheduling the in-office screening procedures. There will not be any web-based questionnaires utilized for pre-screening subjects in this study. All available research staff are responsible for recruiting potential subjects.

After an initial phone screen to determine obvious exclusions from the study protocol, potential subjects will be invited for an in-office visit. During the visit, the study procedures will be described and the subject's questions will be answered prior to obtaining an informed consent. The person obtaining the consent will ask the participant to provide a brief summary of the study to ensure they understand what is being asked of them and any potential risks and benefits.

Veteran and active duty participants may also be recruited for this study through referral from outpatient clinics (VA PTSD Clinics and Medical Clinics-West Haven and the Newington, CT VA Mental Health Clinics, the Brooklyn Campus of the VA NY Harbor Healthcare System, as well as from the Connecticut based ERRERA Community Care Center, Community Based Outpatient Clinics (i.e., Danbury, New London, Stamford, Waterbury, Willimantic, and Winsted) and Vet Centers throughout Connecticut (i.e. New Haven, Hartford, Danbury and Norwich).

F. ***Research Plan and Study Procedures*:**

This is a double-blind, placebo-controlled, 8+ week clinical trial in which patients will be randomized to one of three treatment groups based on the content of their 8 intravenous infusions throughout the study: 0.9% saline (placebo), ketamine (0.2 mg/kg), or ketamine (0.5 mg/kg). On each infusion day, pre-infusion assessment of adverse events and symptom severity will be conducted using a set of clinician- and self-rated scales (see below). Subjects will then receive the ketamine/placebo dose via pump as a 50 mL intravenous infusion administered over 40-minutes based upon randomized treatment assignment. The Research Pharmacy prepares syringes containing 56 mL of drug/placebo (including the 50 mL dose plus 6 mL tubing volume to ensure all the study medication is infused). Possible adverse events (AEs) and mood disturbance symptoms will be assessed repeatedly before, during, and after infusion up to 120 minutes following the study drug administration. At the end of each infusion, clinically significant AEs observed will be recorded in the research record. Subjects will receive 1-2 infusions per week (to assure that no less than 2 calendar days (e.g., Monday & Wednesday; Tuesday & Thursday) and no more than 7 days intervals exist between infusions) for 4+ weeks. A 4-week follow-up period will follow. If an infusion session is missed, it can be made up as long as the 2-day minimum/7-day maximum interval in between sessions is maintained. On each subsequent follow-up visit, possible AE's experienced between visits, will be recorded in the research record. Non-responders (i.e. less than 25% improvement from the baseline CAPS-5 score) at the end of the double-blind treatment period (end of Week 4) will be offered a single infusion of open-label ketamine 0.5 mg/kg. Consistent with the CAP goals, we will collect and bank blood samples at visits 2 (baseline; prior to the first infusion), 3, 7, 11, and 16 for future biomarker analyses.

Dependent Measures: Given the large number of ratings and their compression over time, the gold-standard measurement for PTSD (CAPS-5) would be overly burdensome to the study subjects and may not capture the rapid changes occurring following each ketamine treatment. Instead, similar to the previous report showing the acute effects of ketamine on PTSD symptoms,[24] we have selected the PCL-5 as the primary outcome measure for this study.[28-32] The PCL is a well validated PTSD scale with good internal consistency [29], and test-retest reliability.[33] The PCL strongly correlates with the Clinician-Administered PTSD Scale (CAPS) scores.[31,32,34] The PCL-5 will be obtained at every visit. As a quality control step for the subject self-rated outcome and for diagnostic purposes, we will obtain CAPS-5 scores at baseline, at the end of treatment and at the end of follow-up to correlate with the PCL-5 findings. The index trauma identified at baseline will be evaluated for symptom changes over the course of the trial.

Secondary outcome measures include: The Assessment of Rapid Affect Changes (ARAC), Montgomery-Åsberg Depression Rating Scale (MADRS),[35] Quick Inventory of Depressive Symptoms – Self-Report (QIDS-SR),[36] Patient Health Questionnaire-9,[37] the Generalized Anxiety Disorder-7,[38] Clinical Global Impression Scales,[39] and the Systematic Assessment for Treatment Emergent Effects (SAFTEE),[40] the following assessments will be given throughout the study: Clinician Administered Dissociative States Scale (CADSS)[41],, Positive and Negative Symptom Scale (PANSS)[42], Insomnia Severity Index (ISI),[43] Patient Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance and Sleep-Related Impairment short forms,[44] Snoring, Tired, Observed, Blood Pressure (STOP) Sleep Apnea Screen,[45] West Haven-Yale Multidimensional Pain Inventory (WHYMPI), 3-item numeric rating scale of pain severity,, the Self-Injurious Thoughts and Behaviors Interview (SITBI),[47], Depressive Symptom Index – Suicidality Subscale (DSI-SS),[48],,[49] Veteran's Rand 12-item Health Survey (VR-12)[50], Fagerstorm Test for Nicotine Dependence (FTND) and Fagerstorm Test for Nicotine Dependence – Smokeless Tobacco (FTND-ST); Cogstate, and Quick Drinking Screen (QDS). Assessment intervals are detailed on the study flow chart (Table 2). A brief description of each measure used in the study follows; measures are presented in alphabetical order.

1. Alcohol Use Disorders Identification Test (AUDIT): The AUDIT was developed by the World Health Organization as a brief, 8-item measure that assesses alcohol use over the past year, specifically screening for excessive drinking and some specific consequences of harmful drinking.
2. Assessment of Rapid Affect Changes (ARAC): The ARAC is a 31-item self-report measure assessing affective symptoms (e.g., sadness, guilt, anxious, discouraged, etc.) on a 5 point scale for how the participating is "feeling including right now," where 0 indicates "not at all," 1 indicates "a little bit," 2 indicates "moderately," 3 indicates "quite a bit," and 4 indicates "extremely."
3. Blinding Form – This is a brief form that asks participants their thoughts regarding which treatment arm they were randomized into. This gives us information regarding how successful the research design and research staff were at maintaining the blind.
4. Brief Inventory of Psychosocial Functioning (B-IPF): The B-IPF is a 7-item self-report measure assessing the respondents' level of functioning across seven domains: romantic relationships, relationships with children, family relationships, friendships and socializing, work, training and education, and activities of daily living. Respondents rate the degree to which they had trouble in these domains across the last 30 days.
5. Clinical Global Impressions (CGI) and Patient Global Impressions (PGI): The CGI and PGI are widely used instruments, which assess overall severity of illness on a 1 to 7 point scale with 1 indicating "normal, not at all ill" and 7 indicating "among the most extremely ill patients." These instruments also assess global improvement on a 1-to-7 point scale with 1 indicating "very much improved," 4 indicating "no change" and 7 indicating "very much worse."
6. Clinician-Administered Dissociative States Scale (CADSS): The CADSS contains self and interviewer-administered items including 5 subscales, generated a priori, evaluating dissociation including altered environmental perception, time perception, spatial/body perception, derealization and memory impairment.
7. Clinician Administered PTSD Scale (CAPS-5): The CAPS-5 is a structured interview that corresponds to the DSM-5 criteria for PTSD. The CAPS-5 can be used to make a current (past month) diagnosis of PTSD or to assess symptoms over the past week. In addition to assessing the core PTSD symptoms, questions target the impact of symptoms on social and occupational functioning, improvement in symptoms since a previous CAPS-5 administration, overall response validity, overall PTSD severity, and associated symptoms (depersonalization and derealization).

8. Cogstate: Cogstate is a brief computerized neuropsychological test battery. We will administer the following subtests from this battery to assess working memory, visual motor function, visual attention, executive function, verbal learning/memory and visual learning/memory: One Back and Two Back Test, Chase Test, Identification Task, Groton Maze Learning Test (with delayed recall), the International Shopping List Task (with delayed recall) and the One Card Learning Task. Approximate time to administer these tasks is a total of 30 minutes. Cogstate tasks show no practice effects and are suitable for clinical trials given their short and computerized administration [52,53].
9. Concomitant Medication Log – This is a brief form that allows us to track the medications participants are taking at the time of screening and throughout the study. This includes the medication name and dosing information.
10. Defense and Veterans Brain Injury Center (DVBIC) 3-Item Screening Tool (Brief TBI Screen) / History of Head Injury: The Brief Traumatic Brain Injury Screen, also called the DVBIC TBI Screening Tool, is a 3-question instrument used to evaluate the presence of head injury and related symptomatology. It was validated in a small, initial study conducted with active duty service members who served in Iraq/Afghanistan between January 2004 and January2005.
11. Demographics and Military Service Characteristics Form: The Demographics and Military Service Characteristics Form measures standard demographics (race, gender, age) and military service information (e.g., rank).
12. Deployment Risk and Resiliency Inventory-2 (DRRI-2) Combat Experiences and Postbattle Experiences subscales: The DRRI-2 is a suite of 17 individual scales that assess key deployment-related risk and resilience factors with demonstrated implications for Veterans' long-term health. The Combat Experiences and Postbattle Experiences subscales will be used to assess stressful deployment experiences.
13. Depressive Symptom Index – Suicidality Subscale (DSI-SS): The DSI-SS is a 4-item self-report measure of suicidal ideation that focuses on ideation, plans, perceived control over ideation, and impulses for suicide.
14. Fagerstrom Test for Nicotine Dependence (FTND)/Fagerstrom Test for Nicotine Dependence – Smokeless Tobacco (FTND-ST): The FTND and FTND-ST are both 6-iem self-report measures that assesses severity of nicotine dependence and smokeless tobacco use, subsequently. Questions on both measures probe quantity of nicotine use and pattern.
15. Health Interview: The Health Interview includes items regarding general health, hospitalizations, current and past psychiatric medications, thoughts about wanting to harm others, utilization of mental health services, utilization of outpatient medical services, and caffeine and tobacco use.
16. Generalized Anxiety Disorder-7: This is a 7-item self-report measure to assess and monitor anxiety symptoms and severity. It is widely used as a screener and measure for monitoring generalized anxiety as well as panic, social anxiety and PTSD.
17. Insomnia Severity Index (ISI): The ISI is a 7-item self-report measure that assesses perceived severity of insomnia.
18. Life Events Checklist for DSM-5 (LEC-5): The LEC-5 is a 16-item list of potentially traumatic life events that are commonly associated with PTSD symptoms. For each potentially traumatic event, respondents are asked to rate their experience of that event on a 6-point nominal scale ranging from "1" = happened to me to "6" doesn't apply. This measure is used to facilitate PTSD diagnosis and used in conjuction with the CAPS-5 and PCL-5.
19. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ) is a self-report questionnaire used to determine treatment resistance to antidepressant medications.

20. Mini-International Neuropsychiatric Interview (MINI 7.0): The MINI 7.0 is a short, structured clinical diagnostic interview designed for DSM-V that covers all psychiatric disorders. It is widely used in epidemiological studies and multi-site clinical trials.
21. Montgomery-Asberg Depression Rating Scale (MADRS): The MADRS is a standardized clinical assessment instrument to ascertain depressed mood and neurovegetative signs and symptoms of depression.
22. Pain as the Fifth Vital Sign Numeric Rating Scale (Pain-NRS): The numeric pain score utilized in the VA's Pain as the Fifth Vital Sign initiative relies on an 11-point NRS measure with standardized anchors (0 = "no pain" and 10 = "worst pain imaginable"). Our brief, 3-item measure assesses current pain level, average pain in the past week, and worst pain in the past week.
23. Patient Health Questionnaire-9: This is a 9-item self-report tool for assessing and monitoring depression severity. It is widely used in primary care settings.
24. Patient Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance and Sleep-Related Impairment short forms: This subscale of the PROMIS is a self-report measures assessing sleep disturbance and sleep-related impairment during the past-week.
25. Positive and Negative Symptom Scale (PANSS): The PANSS is commonly used to measure the severity of symptoms in psychotic disorders. It is a clinician-administered scale and includes three categories of symptoms: (1) positive symptoms, such as hallucination and delusion; (2) negative symptoms, such as flat affect and difficulty in abstract thinking; (3) general psychopathology, such as mannerisms and posturing.
26. PTSD Checklist (PCL-5): The PCL-5 is a 20-item self-report measure of the core diagnostic symptoms of PTSD, as described in the DSM-5 for Mental Disorders. The PCL-5 shares similar reliability with the CAPS-5 and has a variety of purposes, including: screening for PTSD symptoms, diagnosing PTSD and monitoring symptom change during and after treatment.
27. Quick Drinking Screen (QDS) Self-Report Version: The QDS is a 4-item measure of alcohol consumption that probes frequency and quantity of consumption.
28. Quick Inventory of Depressive Symptoms-Self Report (QIDS-SR): The QIDS-SR is a 16 item self-report measure designed to assess the severity of depressive symptoms. It is sensitive to change with medications, psychotherapy, or somatic treatments, making it useful for both research and clinical purposes.
29. Self-Injurious Thoughts and Behaviors Interview (SITBI): The SITBI is a structured interview assessing the presence, frequency, and characteristics of self-injurious and suicidal thoughts and behaviors.
30. Snoring, Tired, Observed, Blood Pressure (STOP) Sleep Apnea Screen: The STOP is a 4-item screener used to better understand sleep disturbance in PTSD including sleep apnea.
31. Systematic Assessment for Treatment Emergent Effects (SAFTEE): The SAFTEE systematically assesses for possible treatment-emergent side effects and probes for specific adverse symptoms and documents their severity, relationship to study drug, and the action taken.
32. Veterans Rand 12-item Health Survey (VR-12): The VR-12 is a brief self-report questionnaire for use with Veterans and military personnel, which builds upon the well-established Medical Outcomes Study (MOS) and the Short Form-36 (SF-36) scale. The VR-12 consists of selected items from each of the eight concepts in the SF-36: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, energy/vitality, social functioning, and role limitations due to emotional problems and mental health. Scores are summarized into a physical component and a mental component.
33. West Haven-Yale Multidimensional Pain Inventory-Interference Scale (WHYMPI): The Interference Scale is a 9-item subscale of the larger WHYMPI that measures perceived interference of pain in vocational, social/recreational, and family/marital functioning.

***Clinical Assessments*:** Following informed consent, subjects will undergo the initial screening process, which will involve a comprehensive physical examination and health assessment (e.g. medical and psychiatric history), lab work, an ECG, and standardized psychiatric assessments. Each subject will complete a demographics form to elicit information about the subjects' statistical characteristics, such as education level, socioeconomic status, race and ethnicity. In addition, it will also request information on the subject's family history of mental illness. Participants will have a psychiatric interview conducted by a research clinician. They will also receive a structured diagnostic interview – the Mini-international Neuropsychiatric Interview (MINI)[54] by trained research personnel. Baseline and follow-up ratings will be performed by trained research personnel, whose performance is evaluated routinely in inter-rater reliability sessions. To ensure inter-rater reliability these interview may be audio recorded. These recordings will be assessed by trained diagnostician who is approved study personnel. For those research participants who agree to this explicitly in their informed consent and initial accordingly, de-identified recordings of the clinician administered clinical measures (i.e., CAPS-5, MINI-7, MADRS, CADSS, PANSS) will be uploaded onto the secure database of the CAP and STRONGSTAR per the approved Data Use Agreement (DUA). These recordings will be encrypted and password protected and will include the clinician's name, assessment name, study timepoint, the participants study ID, and the date (e.g., This is Dr. Lynnette Averill administering a CAP-5 for follow-up 2 with CAP7011 on January 25, 2017). The encryption and password will prevent access by non-research personnel. These uploaded recordings will also be used for inter-rater reliability and monitoring clinician drift by the CAP Assessment Core. Clinical ratings are conducted by trained raters who have experience with psychiatric patients. All study raters undergo extensive training; certification and regular calibration exercises under the direction of the CAP Assessment Core and/or the National Center for PTSD Assessment Training Program. Raters at each site must initially conduct interviews under observation by a trained diagnostician in a live interview session and meet agreement. Travel is planned in the first year of the project to allow staff members to visit both sites for training in standardized procedures. Routine audiotaping may also be done during the course of the study in order to confirm ongoing inter-rater reliability and to correct for the potential of rater drift. Consensus discussions regarding difficult cases will be presented for consideration during scheduled conference calls with each site. The primary investigator at each site supervises the administration of clinical measures at the site with oversight from the CAP Assessment Core.

Medical Assessments:

1. Physical exam and health assessment by a licensed physician or Advanced Practice Registered Nurse (APRN).
2. Routine laboratory studies, including: a comprehensive metabolic panel (e.g. electrolytes, hepatic and renal function tests), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and urinalysis. Additional tests will be requested as clinically indicated.
3. Breathalyzer tests will be performed at screening and on test days. The results will be determined before proceeding with any infusions.
4. An ECG.
5. A serum/urine pregnancy test will be administered to all reproductive age females enrolled in the study prior to participation and will be repeated pre-infusion on test days.

Length of Assessment Procedures: It is estimated the screening visit to determine subject eligibility will take 6-7 hours. The CAPS-5 interview will take approximately 1 hour, additional clinician-administered assessments may take up to 20 minutes each. Infusion visits will take approximately 6-7 hours, including assessments, any required medical procedures, the infusion, and post-infusion observation. Follow up visits may take 3-7 hours, depending on which

visit and the requirements (see Table 2 for visit requirements). Some visits may take place over more than one day during the study week, depending on the subject's needs.

Study Drug Administration: Subjects will complete 1-2 infusions per week since test days (i.e. ketamine/placebo infusions) will occur at intervals of no less than 2- and no more than 7-days apart. Following an overnight fast, subjects will receive either 0.9% saline, ketamine 0.2 mg/kg, or ketamine 0.5 mg/kg depending on randomization assignment. All study drugs will be intravenously administered and infused over approximately 40 minutes. Randomization will be stratified by study site (i.e. West Haven and San Antonio) and alcohol use disorder comorbidity.

The entire length of an infusion session will be about 6 hours, so that patients can be prepared for the intravenous infusion, as well as monitored for safety and stability for approximately 2 hours post-start of the infusion. A clinician, who is trained and has significant experience with ketamine infusion studies, will remain in attendance on site during all ketamine infusions. A registered nurse will carry out medical procedures and orders (e.g. IV insertion, study drug administration, assess and record vital signs), and accompany subjects throughout the entire infusion. As part of each drug infusion session, the Positive and Negative Symptoms Scale (PANSS) and the Clinician-Administered Dissociative States Scale (CADSS) will be administered in order to assess for the psychotic and perceptual effects of ketamine, so that we may document the presence and severity of these symptoms and their abatement prior to discharge.

Ketamine regimen justification: In the Mount Sinai study, some PTSD responders maintained the therapeutic benefits from ketamine relative to midazolam for two weeks. However, symptom severity gradually increased between days 3-7 after ketamine.[27] This suggested that repeated infusions might provide sustained clinical benefit, consistent with other repeated dose studies.[21,55] In addition, depression studies have demonstrated the following: 1) The efficacy of twice per week ketamine infusions are comparable to three times per week, 2) 0.2 mg/kg ketamine may possess antidepressant properties with a lower side effects profile, 3) Ketamine is efficacious in patients on stable antidepressant doses, and 4) There is an incremental benefit with repeated ketamine administration and a prolonged duration of treatment response.[21,56-62] Therefore, we have selected a treatment regimen that is predicted to sustain the response observed following single infusion,[27] while testing the dose-related efficacy and longer-term safety of repeated dose ketamine in PTSD. Finally, although a current NIMH-funded trial will investigate the dose-response effect of a single dose ketamine on depressive symptoms in MDD (NCT01920555; Yale is an enrollment site, PI – Sanacora), the results from the depression study will not be sufficient to determine the dose response effects of repeated ketamine in PTSD. Our proposed study will provide critical information about the safety and efficacy of various ketamine doses, which will inform the implementation of ketamine in service-connected PTSD and may provide guidance to the development of novel safe NMDA receptor antagonists.

Blood Collection: We will collect blood samples at visits 2 (baseline; prior to first infusion), 3 (24-hour follow-up #1), 7 (prior to infusion #5), 11 (24-hour follow-up #2), 16 (24-hour follow-up #7). Four tube types at each proposed collection: 1) PAXgene DNA, 2) PAXgene RNA, 3) EDTA plasma tube, and 4) serum separator tube (SST). Standard operating procedures will be followed for blood processing, storage, and shipping.

Blood collection and banking justification: Several biomarkers have been linked to the rapid antidepressant effects of ketamine, e.g. the lower activity "Met" allele of the Val66Met BDNF gene polymorphism show poorer antidepressant responses to ketamine and changes in plasma BDNF levels correlated with treatment response.[59-62] Additionally, ketamine has known anti-inflammatory effects that were recently linked to its antidepressant effects in some preclinical

models 63. The blood collection and banking at the CAP Biomarkers and Genomics Core (San Antonio, TX) will be used to investigate the relationship between ketamine effects on PTSD symptoms and the following blood biomarkers: 1. Val66Met BDNF gene polymorphism; 2. BDNF level, 3. S100B, and 4. Inflammatory markers (TNFa, IL-1b, IL-6, IL-1).

Table 2.

ASSESSMENT / PROCEDURE	VISIT 1	VISIT 2	VISIT 3	VISITs 4-6 ; 8-10	VISIT 7	VISIT 11	VISIT 12	OL FU (post-8th INF/Vst 12.5)	VISITS 13-15	VISIT 16
	SCR	INFUSION 1	FU 1	INF 2,3,4,6,7,8	INFUSION 5	FU 2	FU 3 - OPTIONAL VISIT OPEN LABEL (post-8th infusion)	OL FU	FUs 4-6	FU 7
		DAY 0	DAY 1	DAYS 3, 7, 10, 17, 21, 24	DAY 14	DAY 25	28	29	DAY 35, 42, 49	DAY 56
Adverse Events		X (PRE INF)	X	X (PRE INF)	X (PRE INF)	X	X (PRE INF)	X	X	X
AUDIT	X									
ARAC		X (30, 120)	X	X (30, 120)	X (30, 120)	X	X (30, 120)	X	X	X
B-IPF	X		X			X		X	X	X
CGI		X (PRE INF)	X	X (PRE INF)	X (PRE INF)	X	X (PRE INF)	X	X	X
CADSS		X (30, 120)		X (30, 120)	X (30, 120)		X (30, 120)			
CAPS-5	X					X				X
Concom Med Log	X	X	X	X	X	X	X	X	X	X
Demographics & Military Service	X									
DRRI-2 - Combat	X									
DRRI-2 - Post-Battle	X									
DSI-SS	X	X	X	X	X	X	X	X	X	X
FTND	X		X			X		X	X	X
FTND-ST	X		X			X		X	X	X
GAD-7		X (PRE INF)	X	X (PRE INF)	X (PRE INF)	X	X (PRE INF)	X	X	X
Health Interview	X									X
History of Head Injury (DVBIC)	X									X
Informed Consent*	X									
ISI		X (PRE INF)	X	X (PRE INF)	X (PRE INF)	X	X (PRE INF)	X	X	X
LEC-5	X									X
MGH-ATRQ	X									
MINI-7	X									
MADRS - Full Scale		X (PRE INF)	X	X (PRE INF)	X (PRE INF)	X	X (PRE INF)	X	X	X
MADRS - Item 10 Only	X									
NRS-Pain	X		X			X		X	X	X
PHQ-9	X					X				X
PROMIS (Sleep)	X		X			X		X	X	X
PANSS		X (30, 120)		X (30, 120)	X (30, 120)		X (30, 120)			
PCL-5	X	X (PRE INF)	X	X (PRE INF)	X (PRE INF)	X	X (PRE INF)	X	X	X
PGI		X (PRE INF)	X	X (PRE INF)	X (PRE INF)	X	X (PRE INF)	X	X	X
QDS	X	X			X	X			X (14 only)	X
QIDS-SR	X	X (PRE INF)	X	X (PRE INF)	X (PRE INF)	X	X (PRE INF)	X	X	X
SITBI	X					X				X
STOP	X									
SAFTEE	X	X	X	X	X	X	X	X	X	X
VR-12	X		X			X		X	X	X
WHYMPI	X		X			X		X	X	X
Cogstate	X		X			X		X		X
Physical Exam	X									
Medical History	X									
Routine Lab Tests	X									
Breathalyzer	X	X (PRE INF)	X	X (PRE INF)	X (PRE INF)	X	X (PRE INF)	X	X	X
ECG	X									
Serum Pregnancy Test	X									
Urine Pregnancy Test		X (PRE INF)		X (PRE INF)	X (PRE INF)		X (PRE INF)			
Blood Collection/Banking (e.g., DNA, RNA, Plasma, Serum)		X	X		X	X				X
Vital Signs	X	X (PRE,10, 20, 40)	X	X (PRE,10, 20, 40)	X (PRE,10, 20, 40)	X	X (PRE,10, 20, 40)	X	X	X
Infusion		X		X	X					
Open-Label Infusion							X			
IE Blinding Form						X				
Blinding Form						X				

*No study procedures will be completed prior to completion of the Informed Consent. The "Day" number is an approximation and the actual day may vary depending on delays in prior visits.

Test Days

Screening

Informed consent, physical examination and health assessment, ECG, laboratory tests, concomitant medications, MINI psychiatric assessment, and demographic information.

- Measures including, but not limited to, the DVBIC Brief TBI Screen, CAPS-5, PCL-5, MADRS (item 10 only), QIDS-SR, ARAC, CGI, PHQ-9, GAD-7, AUDIT, ISI, PROMIS Sleep, WHYMPI, Pain-NRS, VR-12, Cogstate, QDS will be administered. Refer to Table 2 for the full battery of measures and administration intervals.
- No more than 200 mL of blood will be collected for routine laboratory tests.
- After completing the screening and being deemed eligible for participation in the study, subjects will be randomized.

Infusion session 1 (Day 0)

- Infusions will take place at Biostudies, nursing/medical coverage will be provided by Dr. Deepak D'Souza group, and will follow all related hospital and Biostudies standard operating procedures and policies.
- Breath alcohol, and urine pregnancy test;
- Blood collection for the biomarkers banking.
- AE Assessment since last visit;
- Intravenous lines started; Vital signs;
- Measures including, but not limited to, the PCL-5, MADRS, QIDS-SR, ARAC, CGI, GAD-7, PHQ-9, QDS, ISI, and will be completed prior to the study drug administration (refer to Table 2).
- Study drug will be infused over 40 minutes.
- Vital signs will be recorded at approximately 10, 20, and 40 minutes during infusion unless closer monitoring is clinically indicated.
- ARAC, CADSS and PANSS will be completed at 30 and 120 min following the start of the study drug infusion.
- Subjects will be observed for at least 2-hours post start of the infusion and may be discharged after being cleared by a study physician/APRN. If intolerable physical or behavioral symptoms persist, they may be admitted to an inpatient unit for further observation and stay overnight if necessary. Subjects will then be discharged with appropriate follow-up care when his or her proximal safety risk is minimal.

Participants will be informed that they may not drive or operate machinery for 12 hours after the end of infusion day procedures, and study staff will ensure that they are picked up by a responsible adult or safely reach their home using alternate transportation.

Follow-up After First Infusion (Day 1)

- A follow-up session will be performed on Day #1. Assessment measures including, but not limited to, the PCL-5, ARAC, MADRS, QIDS-SR, GAD-7, CGI, ISI, QDS, Cogstate, and SAFTEE will be administered (refer to table 2).

- If subjects are unable to make this appointment, they will be contacted by phone 24 hours following study medication dosing, to assess side effects and stability of mood (PCL-5 & QIDS)

Infusion sessions 2-8 (Day 3, 7, 10, 14, 17, 21, 24)

- The protocol will be identical to the first session.
- Procedures for the twice per week infusions will follow the models presented above for the remaining 7 infusion sessions of the study, through Day-24.
- The twice weekly infusions will be scheduled to occur at least 48 hours apart.
- Blood for biomarkers will be collected on Day 14.

Follow-up after infusion session 8 (Days 25, 28, 35, 42, 49, 56)

- Clinical outcomes as detailed in Table 2 will be administered on these follow-up days.
- Blood for biomarkers will be collected on Days 25 and 56
- Following completion of the 4-week follow-up period, study clinicians will continue providing psychiatric care as needed until appropriate referral is arranged.

Open Label Infusion and Follow-up

- Non-responders (i.e., those with less than 25% improvement from the baseline CAPS-5 score) at the end of the double-blind treatment period (end of week 4) will be offered a single infusion of open-label ketamine (0.5 mg/kg). The infusion session procedures will be identical to those noted above. A 24-hour follow-up will also be conducted; the procedures will be identical to the follow-up procedures described above (Refer to Table 2).

Criteria for Discontinuation: Subjects may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a subject from this study are:

- Voluntary discontinuation by the subject, who is at any time free to discontinue his/her participation in the study without prejudice to further treatment.
- Clinical deterioration: The following are objective criteria to trigger full assessment, by the study investigator, for possible discontinuation at the investigator discretion: (a) A 25% increase in the PCL-5 or the CAPS-5 score at any time during the study; (b) Patients with a CGI score ≥ 6 at any post-baseline visit; or (c) the onset of active suicidality as assessed by the study clinicians or by scoring 5 or more on the item-10 of the MADRS.
- Evidence of intolerable adverse reaction, or unable to tolerate study drug.
- Safety reasons as judged by the investigator.
- Stopping birth control or a positive pregnancy test.
- Evidence of problematic alcohol use during the trial.
- Non-compliance to protocol procedures as judged by the investigator.

A subject who discontinues will always be asked about the reason(s) for discontinuation and the presence of any adverse events. If possible, they will be seen and assessed by a study investigator. Adverse events will be followed up as medically necessary.

Data Storage: Paper source documents and research case books will be housed in restricted access files. Personally-identified and protected information (PHI) will be restricted to name, address, phone number, birth-date, social security numbers, dates of care, and will be kept by investigators in a separate file from the research data which will be coded using a subject number assigned by the CAP Data Management and Biostatistics Core at the time of randomization.

Coded data will be key-punch entered by site personnel into the central CAP database housed on FISMA-compliant servers controlled by the CAP Coordinating Center as part of the University of Texas Health Science Center at San Antonio. Audio recordings of the clinician administered clinical measures (i.e., CAPS-5, MINI-7, MADRS, CADSS, PANSS) will also be uploaded digitally into this database for those participants who agree to this in the informed consent. The CAP database servers are compliant with VA Data Security requirements for off-site data storage. This database and its designed security measures have received DoD and VA Central Office approval for offsite data storage for other protocols conducted under the CAP. See additional description of the data storage below in the *Protection against Risks to Confidentiality and Data Security*.

Statistical Consideration: *Group assignment:* Stratified randomization will be used to balance assignment by infusion center, comorbid alcohol use disorder and to decrease the chance of accidental unblinding. The randomization assignment scheme will be developed by the statistician of the study, Dr. Gueorguieva, Co-Director of the CAP Data and Biostatistics Core in collaboration with the Core Director at UTHSCSA (Dr. Jim Mintz). Blinded dose codes will be sent to each of the site pharmacists who will prepare the infusions so as to maintain the double blinding. Both ketamine and saline are odorless and colorless and research staff and subjects will not be able to discern between the placebo and active medication. Ketamine will be stored in the pharmacy according to the procedures for controlled substances and any opened vials will be discarded according to hospital policy. The study drug will be prepared and dispensed by the research pharmacy. Both the rater and the participant will be asked whether they have deduced their treatment arm at the end of each participant's infusion treatments. Blinding will be maintained throughout the study. Dr. Gueorguieva and the CAP Data Management and Biostatistics Core will maintain the list of unblinded assignments for both sites and the research pharmacists will also each have a list of unblinded assignments for their site. Randomization codes will be kept in a secure and locked area within each research pharmacy, where only pharmacy personnel have access. In the case of medical emergency, the blind may be broken by site-designated study personnel by calling the research pharmacist and following standard procedure for caller identification and research study identification.

Sample size justification: Murrough et al. reported large effect sizes (all d's > 1.42) in a study of open-label repeated doses of ketamine for depression.[21] In the recent study of a single infusion of ketamine in PTSD,[27] there was a medium effect size (Cohen's d=0.6) for the comparison between change in PTSD symptoms on ketamine and midazolam from baseline to 24 hours post-infusion. In our study, we expect that the effect size for the comparison between the higher dose ketamine vs. lower dose ketamine will be similar (i.e. Cohen's d=0.6). Furthermore, the effect size for the comparison between the higher dose ketamine and placebo is expected to be much larger (effect size of at least d=0.8) since response on placebo will be smaller than response on an active comparator and our trial has significantly longer duration than the Feder et al. study. This effect size is still much smaller than the estimated effect sizes for the corresponding comparison in subjects with major depression observed by Murrough et al.[21] Based on the effect sizes for the individual comparisons, the expected effect size for the overall treatment by time interaction is medium (Cohen's f=0.24). Thus we estimate that we need 53 subjects per group to test the

primary hypotheses with at least 80% power at two-sided alpha level of 0.05. In particular, with 53 subjects per group we have 87% power to detect a treatment by time interaction of magnitude f=0.24 and 80% power to detect pairwise differences of magnitude d=0.6 or higher at two-sided alpha level of 0.05. Holm-Bonferroni adjustment will be used for the pairwise comparisons and is taken into account in the power calculation so that the family-wise error rate for the pairwise comparisons is kept at 0.05 level. Testing of between group differences over time will be performed within the mixed effects models which are expected to be even more powerful since they use all available data on each individual including data on subjects who dropout or have intermittent missing data due to non-compliance with the treatment schedule. To address potential limitations related to the external validity, we have expanded the age range (18-70), included active duty military personnel and non-OEF/OIF/OND Veterans, and will use stratified randomization to match and balance on study site and alcohol use comorbidity during the trial. Additionally, we plan to track participant duty status, years since trauma and treatment history, and examine these factors in post-hoc analyses.

Analysis plan: Descriptive statistics will be calculated prior to statistical analysis. Distributions of quantitative variables will be assessed for normality using normal probability plots and Kolmogorov-Smirnov statistics and transformations or non-parametric methods will be used as necessary. All statistical tests will be two-sided. Uncorrected alpha level of 0.05 will be used for testing the primary hypothesis as described below. Pairwise post-hoc comparisons and tests of secondary outcome measures will be adjusted using Holm-Bonferroni procedure. Randomized treatment groups will be compared at baseline on potentially confounding factors (e.g. age, sex, history of substance abuse) and variables that are significantly different between groups will be included as additional covariates in the models below. All analyses will be intent-to-treat.

Primary specific aim: To test the dose-related effects of ketamine on PTSD symptoms in Veterans and active duty military population. We will follow our prior PTSD clinical trial,[5] using mixed effects regression models, with group, time, group by time effects for the primary outcome variable (PCL-5). We will stratify by infusion center and alcohol use comorbidity. We do not expect to observe significant differences in treatment effects by infusion center but we will test the interaction of treatment group and infusion center and perform follow-up analyses by site as necessary. Similarly, we do not expect significant moderating effects of alcohol use comorbidity but will assess the interaction between treatment and alcohol use comorbidity and perform follow-up tests as necessary. This approach will be applied to most secondary outcome measures as well. Mixed effects regression models use all available data on each subject, are flexible in modeling the correlation structure of the data and give unbiased results under missing at random assumptions. We will select the best-fitting correlation structure for the primary and each secondary outcome based on Schwartz-Bayesian Information Criterion (BIC). Time will be considered as a categorical predictor and post-hoc tests between groups will be conducted for the change from baseline to end-point, which is of primary interest. To assess the trajectory of ketamine effects over time, we will test for linear, quadratic and higher order time trend differences. Post-hoc tests will also be performed to assess whether dose effects are linear. Change in PTSD symptoms is expected to be the largest for the higher dose ketamine group. However, it is possible that the change in the higher dose ketamine group is not significantly different from the change in the lower dose ketamine group. Thus, we will also estimate effect sizes with confidence intervals for the change from baseline to end-point in each group and use this information together with safety data to inform dose selection for potential future studies of ketamine efficacy and evaluation of mechanism of action in PTSD.

In addition to testing the potential moderating effect of comorbid alcohol use described above, we will also perform exploratory analyses to the assess moderating effects of depression, medication

status, substance abuse, age, and gender by adding these factors one at a time to the models above and testing interactions between each potential moderator and treatment group. We will follow the approach of Kraemer et al. (2002) for testing moderator effects. A secondary analysis of PTSD remission rates (patients in each group who attain a total CAPS-5 score < 23 at the end of the double-blind treatment; i.e. mild/subthreshold PTSD according to CAPS-5 criteria) will be done using two-tailed $\chi 2$ tests in logistic regression analyses that control for site and alcohol abuse comorbidity effects. Dropout rates will be compared across groups and sensitivity analyses using pattern-mixture models will be performed if there are disproportionate dropout rates in the treatment arms of this trial or concerns that the data are not missing at random. Effects of intermittent missing data due to non-compliance with treatment schedule can also be assessed using these models.

Primary efficacy measure justification: After considering alternative measures, we have selected the PCL-5 as the primary outcome measure of this study.[28-32] The PCL is a well validated PTSD scale with good internal consistency,[29] and test-retest reliability.[31,63] While the Clinician Administered PTSD Scale (CAPS) is widely recognized as the gold standard measure to assess efficacy and symptom remission in clinical trials of PTSD, the CAPS is not designed for use in short repeat intervals, such as those incorporated in the present trial (i.e. 24-hours post-infusion) and it would be burdensome for subjects to complete this assessment multiple times over the course of the study, which may also compromise the validity of reports. Additionally, other commonly used short clinician administered instruments, do not accommodate the assessment intervals of the study, may not capture rapid changes associated with medication treatment and some symptoms would produce null results within short time intervals. As a quality control measure for use of the patient rated PCL-5 as a primary outcome instrument, we will repeat the CAPS-5 assessments at the end of treatment and the end of follow-up, and compare these findings to the patient based ratings. Strong correlations have been previously reported between the PCL and the CAPS during validation of the psychometrics for this instrument.[31,32,34]

Exploratory aim 1: Safety of repeated ketamine exposure. 1) Changes in psychotic (PANSS), dissociative (CADSS) and cognitive symptoms (Cogstate) across time between groups will be assessed using mixed effects regression models with group as between-subject factor and time as a within-subject factor as described in the primary specific aim. We anticipate significant differences between ketamine and placebo during infusions but no significant between-group differences at discharge and at the two-week and one month follow-up. 2) Descriptive statistics will be calculated for consumption of recreational substances prior to randomization, throughout the trial and for 4 weeks following the last ketamine exposure. If sufficient sample size is available for analytic modeling of recreational substance use between groups, mixed effects models or nonparametric regression will be used to test for differences between groups. 3) Breath alcohol levels over time will be compared as described for Aim 1. 4) Descriptive statistics will be calculated to summarize types and rates of adverse events between groups. Rates of adverse events will be compared using Fisher's exact tests since numbers of adverse events per arm may be small. Exact logistic regression analyses will be used to assess effects of additional potentially confounding covariates on adverse events if possible (i.e. if sufficient numbers of adverse events are present in the sample to allow for such analysis).

Exploratory aim 2: To assess the durability of ketamine effects on PCL-5, we will use mixed effects regression models in the subjects who responded to the study drug by the end of the double-blind treatment. Week post-treatment will be a within-subject factor and the treatment group a between-subject factor in this analysis, and we will covary for severity at the end of treatment. We will perform pairwise comparisons over time to determine if subjects maintain improvements on ketamine during the 4-week follow-up.

Exploratory aim 3: To test the clinical significance of PCL-5 changes, we will perform secondary mixed model analyses on CAPS-5, CGI, VR-12, PROMIS, WHYMPI, and Pain-NRS, using the same approach as described in Aim 1.

Exploratory aim 4: To test the integrity of the blind, we will use chi-square tests and ANOVA models to compare the accuracy and level of confidence in the guessed treatment assignment between groups.

***Participant Compensation*:** Completion of all study visits is not required for receipt compensation. Subjects will be paid $10/hour, not to exceed $80 for the baseline-screening visit. They will receive $50 per visit for all remaining visits for a possible of 16 visits or $800 and will be reimbursed for transportation based on mileage or receipts provided up to $50 per visit. At the discretion of the investigator, subjects may be reimbursed for additional costs including travel, lodging, parking, transportation, meals, or other expenses. There will be no charge to participants for any aspects of this study including services, testing, evaluation, or medications. Subjects will be informed that they will not receive this compensation if they have outstanding federal debt.

V. POTENTIAL RISKS:

Here we provide a list of reasonably foreseeable risks, including therapeutic risks and research risks. These categories include physical, psychological, social, legal, and privacy risks.

Therapeutic Risks: Subjects participating in this study may temporarily forgo the opportunity for routine psychiatric care. Specifically, we will ask that participants be on stable doses of medications for 4 weeks prior to randomization and, similarly, that they be in a stable routine of psychotherapy for 8 weeks prior to randomization. This will be clearly explained to all participants, along with the treatment strategies that are generally used in patients with PTSD. Following randomization, small changes to doses may be allowable at the PIs discretion and would not be considered cause for discontinuation. We will, of course, ask that they keep study staff informed of any medication or treatment changes. Subjects will also be told that they have a 1/3 chance of receiving placebo, a 1/3 chance of receiving a lower dose of ketamine (0.2 mg/kg) and a 1/3 chance of receiving a higher dose of ketamine (0.5 mg/kg). Subjects will be further informed that following four weeks of double-blind study medication, that they may be offered the option of a single dose of 0.5 mg/kg ketamine if they: 1) Show insufficient response to the study drug (i.e. less than a 25% reduction in their CAPS-5 score) and 2) If they do not have significant side effects. Subjects may continue structured psychotherapy focused on the treatment of their PTSD, if they have been involved in such treatment for at least 8 weeks at randomization.

Delays in starting other treatments and the unproven therapeutic efficacy of study medication in this patient population may mean that subjects' conditions could worsen and lead to increased disturbances in mood, sleep, appetite, and cognition. This could result in loss of work and loss of social functioning. The most serious possible risk is the development of suicidal thoughts and/or behavior, if a subject's condition worsens. Subjects will be closely monitored for suicidality. Pertinent information regarding potential harm, including suicidality, homicidal intent, and ongoing elder or child abuse will be shared as necessary and required by law with clinicians and/or the appropriate authorities. In such circumstances, records may be made available to authorities, even without the subject's consent. Risks should be minimized as there are several safety precautions in place and subjects will remain in close contact with study clinicians.

As previously discussed, females of childbearing potential will likely be enrolled and safeguards

will be instituted (i.e. pregnancy test at screening, prior to each infusion, and requisite use of medically acceptable birth control method), to prevent pregnant subjects from enrolling or subjects conceiving during this investigation.

To control for the potential impact of the therapeutic milieu inherent to an inpatient unit, coupled with the recognition that mandatory inpatient admission would seriously threaten feasibility of recruitment, we propose to conduct the study on an outpatient basis. We believe our stringent selection procedures for study participants (which exclude psychosis, mania, substance use disorder, and active suicidality), as well as our close monitoring throughout the study, enable a safely conducted outpatient study. Additionally, inpatient admission is available to all subjects, if it is clinically indicated.

Research Risk

Screening: The risks and discomforts of the screening and evaluations are minimal. No discomfort is expected to be associated with the physical examination or the intake interview with the study clinician, other than the possible stress of answering personal questions and the risk of loss of privacy and confidentiality, while revealing personal information. Subjects will be answering questions about their symptoms and filling out questionnaires. They may find this process to be inconvenient, uncomfortable or upsetting. The psychological interviews may include personal questions about previous experiences. The questions will be asked in a private room. Subjects will be informed that they do not have to answer any question that they do not want to answer. Subjects will also have the option to discuss their concerns with someone on the research staff. One or more trained individuals will be available to talk to the subjects should they become distressed during an interview or while filling out questionnaires. These assessments have been used without difficulty or adverse events in our previous studies with a similar population. The major disadvantage is the time taken to complete them. Our past experience with these measures indicates that they are acceptable to patients. Additionally, participants found to have a positive breathalyzer for alcohol or positive urine pregnancy screen prior to any study drug infusion will not be allowed to receive treatment that day. The appointment may need to be re-scheduled or the participant may need to be withdrawn from the study for their safety.

Risks of ECG tests: Sometimes the adhesive pads used to attach the leads for recording the electrical activity of the heart can cause skin irritation. Such irritation usually clears without treatment.

Phlebotomy and Intravenous Line Placement: We will draw blood for routine laboratory testing and infuse the study drug. Inserting a needle into a vein is safe when done by professionals under clean conditions. Blood samples are taken from a vein in the inside of the elbow or lower arm. Blood collection is done using a disposable needle or syringe. The risks or side effects associated with taking blood from a vein are bruises, irritation, swelling, bleeding and inflammation. In rare cases, it may result in thrombosis (blood clots) or an infection. Insertion of the needle can cause localized pain or pain at the needle puncture site. Subjects may feel slightly weak or lightheaded, or faint. Occasionally, in rare cases, inserting the needle can result in injury to a nerve. Subjects are closely monitored and checked for these or other symptoms and we will take appropriate measures if they occur. Normally these problems improve with time and no additional medical treatment is needed. Using trained personnel, as well as using sterile conditions minimizes these risks.

Risks associated with blood loss are minimal. No more than 200 mL will be drawn during each blood collection (i.e. routine laboratory tests and 5 biomarkers blood samplings); this represents less than 40% of a 500 mL blood donation. Blood for routine laboratory testing is taken once over

the course of the study (i.e. visit 1/screening) and blood sampling for biomarkers occurs 5 times during the study at visits 2, 3, 7, 11, and 16 (see Table 2).

During the intravenous line placement for study drug, a bruise may occur at the puncture site, and very rarely, an infection may develop or infiltration (i.e. the IV catheter is dislodged and fluid infuses into the tissue) may occur. If this occurs, appropriate treatment will be instituted immediately.

Ketamine: There are side effects associated with ketamine. Most side effects resolve after stopping the drug. The doses of ketamine proposed for this project (0.2 mg/kg and 0.5mg/kg) have been specifically selected to produce mild to moderate behavioral effects without significant sedation. At these doses, ketamine produces a transient alteration of consciousness including altered sensory processing, and thought processes. Initially, subjects frequently feel "drunk" and giddiness is common. As blood levels increase, blood pressure and heart rate increase moderately. This increase is transient and not considered clinically significant. Subjects report differences in complex problem solving evident on frontal lobe and delayed memory tasks, some subjects may report a narrowing of their concentration, feeling distant from surroundings, and enhanced perception of some sensory stimuli. Subjects sometimes report blurred vision and nystagmus. Alterations in the perception of time, body boundaries, and illusions occur. Subjects may experience visual distortions, altered perception of orientation in space, and inability to control thought processes. Subjects may report feeling quite distanced from their surroundings, describe altered awareness of their bodies, and they may close their eyes. During this period, they are still oriented to time and place. They can complete ratings scales testing memory without impairment, their rate of finger tapping is unchanged and the latency of their response on continuous performance tasks of attention is not increased. However, some individuals feel that they cannot control the experience and find it frightening. Vivid dreams and poor sleep quality after infusion of ketamine has also been reported, although dream content was not necessarily unusual and alterations in sleep were not reported on subsequent nights.

The dose used in this study will produce blood levels that are 1/20 to 1/5 of those produced clinically when ketamine is used as an anesthetic. Short-term safety data showed that adverse events in response to ketamine infusion have been mild and transient; with no evidence of any clinically significant or persistent adverse effects (65). Adverse events included nausea and vomiting, sedation, headaches, anxiety, paranoia, hypotension, insomnia and nightmares and transient pain in the infusion arm. Adverse events reported at the full anesthetic level doses (1-4.5 mg/kg) of ketamine include: Greater than 10%: Emergence symptoms, hypertension, increased cardiac output, increased intracranial pressure, tachycardia, tonic-clonic, movements, visual hallucinations, vivid dreams. Between 1-10%: bradycardia, diplopia, hypotension, intraocular pressure, injection site pain, nystagmus. Less than 1%: Anaphylaxis, cardiac arrhythmia, depressed cough reflex, fasciculations, hypersalivation, intraocular pressure, increased metabolic rate, hypertonia, laryngospasm, respiratory depression or apnea with large doses or rapid infusions. Other adverse events may include gastrointestinal disturbances, dizziness, and rash. A member of the research team will continuously monitor the participant during the infusion process IAW local policies and procedures to identify any acute and/or persistent alterations in health status that would warrant medical attention.

Ketamine in Pregnancy: Ketamine has not been formally assigned to a pregnancy category by the FDA. The safe use of ketamine during pregnancy has not been established and the recommendation from the manufacturer is for ketamine not to be used. Women who are breastfeeding will be excluded from enrollment. If a woman becomes pregnant during the study, the study medication will be discontinued.

Privacy Risks: Subjects will be answering personal questions about their symptoms and filling out questionnaires. They may find this process to be inconvenient, uncomfortable or upsetting. The psychological testing may include personal questions about previous experiences. The questions will be asked in a private room. The research staff will inform subjects that they do not have to answer any question that they do not want to answer and all reported data will only be identifiable by subject identification number. The personal health information obtained under this study will be stored in a FISMA-compliant server approved by VA data security and as hardcopies in locked, restricted-access file cabinets. Only designated study personnel will have access to this information. VA subjects will be informed that their name and social security number will appear on payment vouchers that will be sent to the VA Fiscal Service and the Agent Cashier for approval and reimbursement. Subjects will be further informed that medical evaluations, including physicals, ECGs, and urine/blood tests will be administered through their VA and DoD hospitals and will become part of their permanent record. Finally, subjects will be informed that a hard copy of the consent form will be placed in their paper record. Electronic progress notes citing subjects' participation in this research study will be entered in their VA and DoD electronic medical records upon entry into and exit from, the study.

Pertinent information regarding potential harm, including suicidality, homicidal intent, and ongoing elder or child abuse will be shared as necessary and required by law with clinicians and/or the appropriate authorities. In such circumstances, records may be made available to authorities, even without the subject's consent.

Participation in this study may also involve risks that are not known at this time.

Minimizing Risks: We describe below the manner in which the above-mentioned risks will be minimized.

Informed Consent: Following patient assent, eligibility will be first assessed via telephone screening and if records are available, by a preliminary medical record review. If the subject seems to be a likely candidate for inclusion in this protocol, he or she will be evaluated for study eligibility in person. Telephone screens will be done by experienced research personnel adept with this process. Following a face-to evaluation and discussion with the research team, an experienced study clinician and/or co-investigator will determine suitability for enrollment and randomization.

A release of information may be obtained for review of any available historical and clinical data outside of the VA/DoD settings, as well as to talk with current treatment providers prior to initiating study medication. A written authorization form is obtained from each subject, permitting the research team to use, create, or disclose the subject's PHI for research purposes and the informed consent procedures comply with the standards of the Institutional Review Boards. The nature of the project, procedures, relative risks and benefits, and alternatives to participation in the project are discussed with all participants by trained and knowledgeable research personnel. Following this discussion, the subject is given a copy of the consent form to review at his/her leisure, and any questions are answered. The potential subject is asked to communicate a reciprocal understanding of the protocol. This "say back" method has demonstrated reliability among educators in ascertaining the degree of comprehension. If the subject is interested in the project, written informed consent is obtained and medical and psychiatric screening procedures are undertaken to confirm eligibility. If the subject decides not to participate in this study, the decision not to participate does not affect eligibility to participate in future studies or to receive treatment from their local VA/Military Medical Center or any collaborating treatment facility, or to receive treatment on a private basis from a referring

clinician. Participants are free to withdraw consent and study participation at any time during the trial.

Subjects recruited into this study may have had prior contact with research clinics and/or may have participated in a prior approved experimental protocol. An approved research staff member who was not working with the subject during the routine clinic assessment will explain the risks and benefits of study participation and obtain informed consent from the subjects. However, there may be some overlap in the research and clinical staff who interview, test, and conduct the assessments with the subjects. Subjects will be told that their participation in research has no impact on the clinical services available to them.

Protection against Risks to Confidentiality and Data Security: Research personnel will collect study data via direct interview and through clinical and medical procedures. This data will be recorded in both written and/or electronic formats. All electronic resources will be encrypted and password-protected to preclude access by non-research personnel. All electronic PHI (ePHI) will continue to be encrypted and password-protected after subject participation. Without repository consent to the contrary, both written and ePHI will be destroyed after the protocol is completed at a time designated by the institutional polices and the primary investigators. All electronic data will be stored on FISMA-compliant central computers maintained by the CAP Coordinating Center. The project uses two Dell Servers, both with RAID configured multiple hard drives as well as a separate external daily backup. The physical layer of the internal network infrastructure is a Gigabit Ethernet backbone maintained by university networking resources. The University network is then subdivided into Virtual Local Area Networks (VLANs) to better control network access and isolate high-risk computer systems and services. Access to the database website is restricted to SSL (128 bit) encrypted connections and authentication is by username and password. The password is hashed (one-way-encrypted) using MD5 encoding so it is nearly impossible to reverse engineer the hash and get a person's password. The servers are on a backup power supply and are behind a locked door with a combination lock. Access is restricted to key IT personnel in the CAP Data & Statistics Core. A Dell tape library (Ultrium tapes) provides primary backup on a nightly basis. Primary physical security for the network is provided by University Telecommunications & Networking. The University provides a series of CISCO firewalls and switched routers to provide the first line of campus security. Additionally, an external agency is responsible for monitoring firewall activity and event logs to provide an independent analysis of intrusion attempts and trends. Network Design: The University has subdivided its network into Virtual Local Area Networks (VLANS). A user must be physically mapped into a VLAN before any resources may be accessed.

All data reports prepared for this study will protect subject confidentiality. Paper research records are coded by a subject ID number and stored in locked cabinets. Consent forms, HIPAA forms, enrollment logs, and release of information forms will be kept locked in a place separate from subject data collection forms.

This data will only be made available to the investigators and other research personnel, auditing regulatory agencies, an independent, appointed research study monitor and the institutional IRBs. Each site will, respectively, seek IRB approval to put HIPAA identifiers in a VA and DoD-approved database with procedures to separate these identifiers from the coded-dataset. This data will be destroyed after closure of the study unless we have a data repository and related informed consent to retain the data. Additional confidentiality measures follow the procedures and institutional policies of each site. These policies have proven to be effective within the VAHC and DoD systems for the protection of data security.

Protection against Risks to Subject Safety: Subjects will be informed of any important discoveries

made during the study, which may affect their condition or willingness to continue participation. Subjects will either be informed of the new information in person or by letter, if the subject cannot be reached in person.

a. ***Ketamine*** has been administered to over 10,000 patients and reported in greater than 100 individual research investigations, including many over the past three decades from our research group. Since 1989, we have administered ketamine on over 800 occasions to over 300 subjects. Our group pioneered ketamine studies in healthy subjects,[64-71] and in depression,[6,72,73] and we have extensive experience in ensuring participants' safety.[74] Ketamine has a wide margin of safety and is typically provided in doses of 1-4.5 mg/kg IV over 1 minute as a sole anesthetic agent. In the majority of psychiatric investigations in depressed subjects to date, ketamine has been administered at subanesthetic doses (typically 0.5mg/kg) infused over 40 minutes. Based on extant literature using subanesthetic doses of ketamine in a medical setting, it has been demonstrated that the acute psychomimetic and temporary perceptual disturbances that may follow ketamine infusion and its potential to exacerbate trauma recall post-infusion, are transient in nature starting within minutes of ketamine infusion and lasting less than 2-hours post-infusion.[74] In considering the implications of these adverse effects, it is important to note the consistent evidence that these temporary symptoms are dose-dependent with increased prevalence of symptoms at higher doses of ketamine.[68,75,76] Members of our research team have administered doses exceeding 0.5 mg/kg of ketamine to healthy subjects and have successfully managed the transient nature of side-effects at this lower-dose.[64-67,77,78] The dosages of ketamine selected for this clinical trial (0.5 mg/kg and 0.2 mg/kg infused over 40 minutes) produces blood levels that are 1/20 to 1/5 of those produced clinically when ketamine is used as an anesthetic.

Study infusion will be done in a medical setting, with continuous monitoring of respiratory and cardiac function (i.e., vital signs) will be done. Crash carts are available on the unit with medical personnel for immediate availability of resuscitative drugs and equipment in the event of an unexpected adverse drug reaction Safety measures also include possible discontinuation of the study drug and transition to standard clinical treatment, should subjects worsen to a sufficient degree. In case of a medical emergency, the medication group blinding can be broken by the principal investigator, designated covering staff member or the research pharmacist, in order to supply information required for emergency medical care of research subjects. All subjects will be given a "wallet card" which identifies them as a study participant and lists the emergency contact numbers. If a subject shows clinical deterioration (worsening of PTSD symptoms), the study physician/APRN will determine whether: 1) the subject can remain in the study, or; 2) a higher level of care (e.g. referral back to treating psychiatrist or referral to emergency or inpatient care) is needed.

b. ***Suicidal Ideation and Imminent Harm***: Office visits occur 1-2 times per week (i.e., infusions and follow-up visits as appropriate per protocol) throughout the treatment part of the clinical trial including phone calls during any week with missed study visits, to help ensure subject safety and protocol adherence. Study clinicians and raters ask patients about any new symptoms experienced at every visit and will assess subjects at each visit for suicide risk and potential. All communications about suicide and threats are taken seriously. Individuals at such risk will be treated appropriately, including options such as increased contact, more frequent clinical visits, or emergent psychiatric hospitalization. Subjects who score > 5 on the MADRS item 10 (suicide) at screening will be excluded from the study. In addition, an inability to control suicide attempts, imminent risk of suicide in the investigator's judgment, or a history of serious suicidal behavior. Throughout the study, any subject who presents with increased suicidality will be fully assessed for discontinuation (see above for discontinuation criteria). The study clinicians also reserve the right to complete the SITBI and DSS-IS at any point throughout the study if there are concerns

about a subject's suicidal ideations.

All clinical staff associated with ratings have experience in psychiatric assessment and will implement protocol procedures in a sensitive and supportive manner. Interviews will be stopped if subjects become distressed or object to answering questions. In summary, measures to minimize risks include:

- Before participating, subjects undergo careful psychiatric and medical evaluation.
- An experienced research nurse and study clinician are available at all times during the infusion sessions to provide medical monitoring, support and consistent "reality testing" for individuals experiencing confusion or transient psychosis. Subjects will be debriefed; a review of the test day will be done with subjects to evaluate emotional response and to monitor adverse reactions to before they leave.
- If a subject reports that symptoms cannot be tolerated, the study drug infusion will be stopped.
- Subjects will be observed for 2 hours after the start of the infusion, and if intolerable physical or behavioral symptoms persist, they will be discontinued from the study. Subjects will then be treated as clinically indicated.
- Subjects will be informed that they may not drive or operate machinery for 12 hours after the end of test day procedures, and study staff will ensure that they are picked up by a responsible adult or safely reach their home on alternate transportation. They will also be advised to not engage in demanding work in the day following the test sessions. We will work with subjects to schedule the test days accordingly.
- Subjects will be provided a number to call to reach an on-call research psychiatrist (available 24 hours/day) should unpleasant effects occur after subjects have left the testing facility. They will also be provided with wallet cards identifying their participation in this study, should the research pharmacist need to break the study blind.
- If necessary, subjects will be administered IV lorazepam to reduce residual symptoms and their participation in the study will be terminated. Such subjects will be monitored as found appropriate by the study clinicians.
- In an effort to minimize risks, subjects with active suicidal ideation or recent self-injurious behavior will be excluded. During treatment phase, all subjects will be scheduled at our research clinic at a minimum of once to twice per week visits for ongoing assessment of behavioral symptoms as per protocol (e.g., infusion visits and follow-ups as appropriate).
- If a subject's clinical condition significantly worsens, he or she will be discharged from the research protocol and referred for treatment in the most clinically appropriate setting.
- Study participants will be informed that a decision to initiate standardized psychotropic and/or psychotherapeutic regimens will not adversely affect their ability to participate in future protocols or receive treatment at any VA facilities.
- Subjects will continue to be followed weekly for 4 weeks following the last study infusion day. During these follow-up visits, patients will be evaluated for adverse events and complete psychiatric and medical symptom rating scales. Following completion of this 4-week follow-up period, study clinicians will continue providing psychiatric care as needed until appropriate referral is arranged.

These precautions are likely to be highly effective in minimizing risks. If a subject discontinues study medication, he/she will receive standard clinical treatment as indicated. If treatment is terminated due to adverse events or physical risks, subjects will be followed carefully until resolution of symptoms and treated with follow-up care as clinically indicated.

Possible Benefits:

Subjects may not receive any benefit from participating, although their participation may help patients in the future by giving important information about the study medication and PTSD. Subjects may benefit from initial screening procedures that will include a careful examination of their medical and psychiatric conditions. In the event that clinical abnormalities are discovered, subjects will be informed of the findings and referred for appropriate care.

Although preliminary studies show a rapid and potent antidepressant effect in depressed patients following ketamine administration, about 50% of subjects did not respond to ketamine and for those who responded, the antidepressant effect was maintained for about one week in most studies. Nonetheless, we cannot and do not guarantee or promise that a PTSD subject will receive any direct health benefits from participating in the study. Study personnel will offer a referral to treatment after completion of this study. However, the potential benefit is to society at large, as the knowledge gained from these studies may help also people with PTSD and depression by contributing to our understanding of these illnesses and their treatments. All participants in this study may derive subjective benefit from volunteering to take part in a study for the advancement of scientific knowledge. The relative risks and inconveniences associated with participation in this study are balanced by the potential benefits to society, particularly patients suffering from PTSD.

VI. Data Safety Monitoring Plan: An independent data safety monitoring board will be established by the CAP Coordinating Center for this trial and will have the authority to review unblinded results. As above, we will also have an IRB appointed and approved independent research monitor. This Research Monitor, Dr. Mohini Ranganathan, M.D., Psychiatrist at the VA Connecticut Healthcare System, is responsible to oversee the safety of the research and report observations/findings to the IRB or a designated institutional official. The Research Monitor will review all unanticipated problems involving risks to subjects or others associated with the protocol and provide an independent report of the event to the IRB. The Research Monitor may discuss the research protocol with the investigators; shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report; and shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the USAMRMC Human Research Protection Office (HRPO).

Additionally, in coordination with the CAP Director of Research and the CAP Regulatory Coordinator, the protocol will be reviewed and approved by the appropriate regulatory oversight organizations including: the VA Connecticut Healthcare System Human Subjects Subcommittee, the VA Research & Development Committee; the University of Texas Health Science Center Institutional Review Board (IRB); the Brooke Army Medical Center IRB that reviews for the San Antonio Military Medical Center; and the USAMRMC Human Research Protection Office (HRPO) to satisfy all federal and VA regulatory requirements for human subject protections in accordance with all Title 21, 32, and 45 Codes of Federal Regulations (CFRs) pertaining to issues in the ethical conduct of research. The CAP Data & Safety Monitoring Plan will guide ongoing data and safety monitoring in the following ways:

1) Ongoing communications will occur with all regulatory oversight entities to ensure all reporting requirements are met including: protocol deviations, continuing reviews, protocol amendments, summary reports of trial progress, adverse events (AEs), serious adverse events (SAEs), and unanticipated problems involving risk to subjects or others (UPIRSOs).

2) Personnel will be trained in the processes for the assessment of AEs in human subjects and AE monitoring, PI-review, and regulatory reporting will occur at both sites with ongoing communications with regulatory oversight agencies[80].

The investigator's assessment of the overall risk for subjects participating in this study is moderate.

Moderate Risk DSMP

1. Personnel responsible for the safety review and its frequency:

The principal investigators at each site are responsible for monitoring study data, assuring protocol compliance, and conducting the safety reviews at the specified frequency, which must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. The principal investigator, the IRB, the IRBs appointed Research Monitors, the CAP Coordinating Center, and/or the Data Safety Monitoring Board (DSMB) have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed moderate for the following reasons:

- We do not view the risks associated with ketamine as minimal.
- Given the established safety and validity of the use of ketamine, we do not view the proposed study as high risk.

Although we have assessed the proposed study as one of moderate risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study on site as follows:

3. Attribution of Adverse Events:

Adverse events (AEs) are defined any untoward, physical, social, economic or psychological occurrence affecting human subjects in research. An AE can be any unfavorable or unintended event including abnormal laboratory finding, symptom, reaction, or disease. An AE does not necessarily have a causal relationship with the research, or any risk associated with the research, the research intervention, or the assessment. Adverse events involve subjects only.

AEs will be monitored for each subject participating in the study. Separate and apart from the determination that an AE has occurred, the site investigators will determine their attribution to the study procedures / design according to the following categories:

a. **Related**: Adverse event is reasonably regarded as caused by the research.
b. **Probably**: Adverse event is likely caused by the research.
c. **Possibly**: Adverse event may be caused by the research.
d. **Unlikely**: Adverse event is likely not to be caused by the research.

e. Unrelated: Adverse event is clearly not caused by the research

4. Plan for Grading Adverse Events:

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event (does not affect patient activity)
2. Moderate adverse event (mild disruption in usual activity)
3. Severe (major disruption in usual activity)

5. Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events: In addition to grading the adverse event, adverse events are evaluated to determine whether they meet the criteria for a Serious Adverse Event (SAE). An SAE is defined as death; a life threatening experience; inpatient hospitalization (for a person not already hospitalized); prolongation of hospitalization (for a patient already hospitalized); persistent or significant disability or incapacity; congenital anomaly and/or birth defects; or an event that jeopardizes the participant and may require medical, surgical or other intervention to prevent one of the preceding conditions (FDA, 21 CFR Part 312).

An adverse event is considered serious if it:

1. is life-threatening
2. results in in-patient hospitalization or prolongation of existing hospitalization
3. results in persistent or significant disability or incapacity
4. results in a congenital anomaly or birth defect OR
5. results in death
6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, or
7. adversely affects the risk/benefit ratio of the study

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRBs and the data safety monitoring board is necessary.

Unanticipated Problems Involving Risk to Subjects or Others (UPIRSOs). Every AE is evaluated as a possible UPIRSO so as to support the prompt reporting requirements of UPIRSOs. These events are defined as:

a. "Possibly related" or "probably related" or "related" to participating in the research ("possibly" related means there is a reasonable possibility that the AE may have been caused by the procedures or intervention of the study) meaning that you can't say "not related" or "unknown."
b. Unexpected (in terms of nature, severity, or frequency) given:
    1. The research procedures described in the IRB-approved research protocol and /or informed consent document; or

2. The known characteristics of the subject population or disease condition being studied;

c. UPIRSO's involve a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized or approved by the IRB.

6. Plan for reporting AEs, SAEs, and UPIRSOs to the IRBs, the CAP Coordinating Center, the Human Research Protections Office (HRPO), and the Data Management Committee (DMC)

The investigator is responsible to monitor safety and record the results of that monitoring in the form of an Adverse Events (AE log). The principal investigator (or designated medical co-investigator) will conduct a review of all AEs upon completion of every study subject and will evaluate the frequency and severity of the adverse events, in order to determine if modifications are required to the protocol or consent forms.

The investigators will report AE's, SAE's, and UPIRSOs to their respective IRBs according to local policies and reporting procedures.

As part of the CAP, additional reporting requirements to the DMC, other IRBs with jurisdiction, and HRPO will be fulfilled by the CAP Coordinating Center Regulatory Coordinator.

VI. Informed consent: A waiver of written informed consent and HIPAA authorization is requested for a pre-screening phone interview and medical record review. Following the phone screen, if an individual appears to meet enrollment criteria and is interested in participating, the subject is invited for a face-to-face interview and the written informed consent and HIPAA authorization is obtained by one of the project investigators. A release of information may be obtained for review of any available historical and clinical data. A written authorization form is obtained from each subject, permitting the research team to use, create, or disclose the subject's PHI for research purposes. PHI that may be collected as part of this study includes participants' name, address, contact information, Social Security Number, Date of Birth, VA/DoD Medical Record Numbers, and dates of study visits. The nature of the project, procedures, relative risks and benefits, and alternatives to participation in the project are discussed with the individual. Following this discussion, the individual is given a copy of the consent form to review at their leisure, and any questions are answered.

If the individual is interested in the project, written informed consent is obtained, and medical and psychiatric screening procedures are undertaken to confirm eligibility. A copy of the consent form is provided to all participants. If the individual decides not to participate in this study, the decision not to participate does not affect eligibility to participate in future studies, to receive treatment at each site or any affiliated facility or to receive treatment on a private basis from a referring clinician.

VI. Confidentiality: Reports generated from this study will not contain any identifying information about the participants. Research records are coded only by a number, and are stored in locked cabinets. Consent forms, HIPAA forms, enrollment logs and release of information forms will be kept locked in a place separate from subject data collection forms. Finally, subjects will be informed that a hard copy of the consent form will be placed in their paper record.

VIII. Location of Study: This study will be conducted at two sites, the West Haven, CT VACHS and the San Antonio Military Medical Center (SAMMC) through its affiliation with the CAP at the University of Texas Health Sciences Center located in San Antonio, TX.

IX. Source of Funding: VA and DoD (W81XWH-13-2-0065 to the University of Texas Health Science Center and a subcontract to Yale University) through the Consortium to Alleviate PTSD (CAP).

X. Probable duration: The study will be conducted over 5 years.

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