NCT02727998

Intensive 7-day Treatment for PTSD Combining Ketamine With Exposure Therapy

08FEB2021

YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Biomedical Research
100 FR1 (2015-1)

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: Combining neurobiology and new learning: Ketamine and Prolonged exposure: A potential rapid treatment for PTSD			
Principal Investigator: Ilan Harpaz-Rotem		**Yale Academic Appointment:** Associate Professor	
Department: Psychiatry			
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Campus Phone: 2039374760	**Fax:**	**Pager:**	**E-mail:** ilan.harpaz-rotem@yale.edu
Protocol Correspondent Name & Address (*if different than PI*): Kristin DeFrancesco, 2 CSS, Suite 401, New Haven, CT 06519 (through initial approval) Charles Gordon, 950 Campbell Ave, West Haven, CT 06516-2770 (after initial approval)			
Campus Phone: Kristin : 203-785-3852 Charles : 203-932-5711	**Fax:**	**E-mail:** kristin.defrancesco@yale.edu charles.gordon@yale.edu	
Yale Cancer Center CTO Protocol Correspondent Name & Address (*if applicable*):			
Campus Phone:	**Fax:**	**E-mail:**	
Business Manager:			
Campus Phone :	**Fax :**	**E-mail**	

Faculty Advisor:(required if PI is a student, resident, fellow or other trainee) ☒ **NA**		**Yale Academic Appointment:**	
Campus Address:			
Campus Phone:	**Fax:**	**Pager:**	**E-mail:**

Investigator Interests:

Does the principal investigator, or do any research personnel who are responsible for the design, conduct or reporting of this project or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual's role and

degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

See Disclosures and Management of Personal Interests in Human Research
http://www.yale.edu/hrpp/policies/index.html#COI
❑ Yes X No

Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?
❑ Yes X No

If yes to either question above, list names of the investigator or responsible person:

The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current financial disclosure form on file with the University's Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as co-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form: http://www.yale.edu/coi/

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. **Whether or not they are required to maintain a disclosure form with the University's Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.**

SECTION II: GENERAL INFORMATION

1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

a. Internal Location[s] of the Study:

☒ Magnetic Resonance Research Center (MR-TAC)
☐ Yale Cancer Center/Clinical Trials Office (CTO)
☐ Yale Cancer Center/Smilow
☐ Yale-New Haven Hospital
☐ Cancer Data Repository/Tumor Registry
☐ Yale University PET Center
☐ YCCI/Church Street Research Unit (CSRU)
☒ YCCI/Hospital Research Unit (HRU)
☐ YCCI/Keck Laboratories
☐ Yale-New Haven Hospital—Saint Raphael Campus
☒ Specify Other Yale Location: 300 George St. (Decision Neuroscience Lab)

b. External Location[s]:

☐ APT Foundation, Inc.
☐ Connecticut Mental Health Center
☐ Clinical Neuroscience Research Unit (CNRU)
☐ Other Locations, Specify:
☐ Haskins Laboratories
☐ John B. Pierce Laboratory, Inc.
☐ Veterans Affairs Hospital, West Haven
☐ International Research Site
(Specify location(s)):

c. Additional Required Documents *(check all that apply)*: ☐ N/A

☐ *YCCI-Scientific and Safety Committee (YCCI-SSC) Approval Date:
☐ *Pediatric Protocol Review Committee (PPRC) Approval Date:
☐ *YCC Protocol Review Committee (YRC-PRC) Approval Date:
☐ *Dept. of Veterans Affairs, West Haven VA HSS Approval Date:
☐ *Radioactive Drug Research Committee (RDRC) Approval Date:
☐ YNHH-Radiation Safety Committee (YNHH-RSC) Approval Date:
☒ Magnetic Resonance Research Center PRC (MRRC-PRC) Approval Date: 8/26/2015
☐ YSM/YNHH Cancer Data Repository (CaDR) Approval Date:
☐ Dept. of Lab Medicine request for services or specimens form
☐ Imaging on YNHH Diagnostic Radiology equipment request form (YDRCTO request) found at http://radiology.yale.edu/research/ClinTrials.aspx)

Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.
   The anticipated duration of the project is 5 years.

3. **Research Type/Phase: (Check all that apply)**
   a. **Study Type**
   ☒ Single Center Study
   ☐ Multi-Center Study
   Does the Yale PI serve as the PI of the multi-site study? Yes ☐ No ☐
   ☐ Coordinating Center/Data Management
   ☐ Other:

   b. **Study Phase** ☐ **N/A**
   ☐ Pilot ☐ Phase I ☒ Phase II ☐ Phase III ☐ Phase IV
   ☐ Other (*Specify)*

4. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

☒ Clinical Research: Patient-Oriented ☐ Clinical Research: Outcomes and

☐ Clinical Research: Epidemiologic and Behavioral
☐ Translational Research #1 ("Bench-to-Bedside")
☐ Translational Research #2 ("Bedside-to-Community")
Health Services
☐ Interdisciplinary Research
☐ Community-Based Research

5. Is this study a clinical trial? Yes ☒ No ☐

NOTE the current ICMJE (International Committee of Medical Journal Editors) definition of a clinical trial: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events"

If yes, where is it registered?

Clinical Trials.gov registry ☒
Other (*Specify*)

*Registration of clinical trials **at their initiation** is required by the FDA, NIH and by the ICMJE.*

If this study is registered on clinicaltrials.gov, there is new language in the consent form and compound authorization that should be used.

For more information on registering clinical trials, including whether your trial must be registered, see the YCCI webpage, http://ycci.yale.edu/researchers/ors/registerstudy.aspx or contact YCCI at 203.785.3482)

6. Does the Clinical Trials Agreement (CTA) require compliance with ICH GCP (E6)?
Yes ☐ No☒

7. Will this study have a billable service? *A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects*.

Yes ☒ No☐

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

8.. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes _X_ No __ *If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*
a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? Yes.
b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? No

c. Will a novel approach using existing equipment be applied? No

If you answered "no" to question 8a, or "yes" to question 8b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. ***By signing this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH****.*

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

1. **Funding Source:** Indicate all of the funding source(s) for this study. Check all boxes that apply. Provide information regarding the external funding source. This information should include identification of the agency/sponsor, the funding mechanism (grant or contract), and whether the award is pending or has been awarded. Provide the M/C# and Agency name (if grant-funded). If the funding source associated with a protocol is "pending" at the time of the protocol submission to the HIC (as is the case for most NIH submissions), the PI should note "Pending" in the appropriate section of the protocol application, provide the M/C# and Agency name (if grant-funded) and further note that University (departmental) funds support the research (until such time that an award is made).

PI	Title of Grant	Name of Funding Source	Funding	Funding Mechanism
Ilan Harpaz-Rotem	Combining neurobiology and new learning. Ketamine and Prolonged exposure: A potential rapid treatment for PTSD	Clinical Neuroscience Division, National Center for PTSD Yale School of Medicine, Department of Psychiatry	☐ Federal ☐ State ☒ Non Profit ☐ Industry ☐ Other For Profit ☐ Other	☐ Grant-M# ☐ Contract# ☐ Contract Pending ☒ Investigator/Department Initiated ☐ Sponsor Initiated ☐ Other, Specify:

			☐ Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For Profit ☐ Other	☐ Grant-M# ☐ Contract# ☐ Contract Pending ☐ Investigator/Department Initiated ☐ Sponsor Initiated ☐ Other, Specify:
			☐ Federal ☐ State ☐ Non Profit ☐ Industry ☐ Other For Profit ☐ Other	☐ Grant-M# ☐ Contract# ☐ Contract Pending ☐ Investigator/Department Initiated ☐ Sponsor Initiated ☐ Other, Specify:

IRB Review fees are charged for projects funded by Industry or Other For-Profit Sponsors. Provide the Name and Address of the Sponsor Representative to whom the invoice should be sent. ***Note: the PI's home department will be billed if this information is not provided.***

Send IRB Review Fee Invoice To:

Name:
Company:
Address:

2. **Research Team:** List all members of the research team. Indicate under the affiliation column whether the investigators or study personnel are part of the Yale faculty or staff, or part of the faculty or staff from a collaborating institution, or are not formally affiliated with any institution. **ALL members of the research team MUST complete Human Subject Protection Training (HSPT) and Health Insurance Portability and Accountability Act (HIPAA) Training before they may be listed on the protocol. See NOTE below.**

Listed in IRES IRB

NOTE: The HIC will remove from the protocol any personnel who have not completed required training. A personnel protocol amendment will need to be submitted when training is completed.

SECTION IV: PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR AGREEMENT

As the **principal investigator** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean's Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital, or have a faculty advisor.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities.

Ilan Harpaz-Rotem,
PI Name (PRINT) and Signature

Date

As the **faculty advisor** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- This project has scientific value and merit and that the student or trainee investigator has the necessary resources to complete the project and achieve the aims.
- I will train the student investigator in matters of appropriate research compliance, protection of human subjects and proper conduct of research.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- The student investigator will obtain approval for this research study and any subsequent revisions prior to initiating the study or revision and will obtain continuing approval prior to the expiration of any approval period.
- The student investigator will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set forth by the University and qualify to serve as the faculty advisor of this project.
- I assume all of the roles and responsibilities of a Principal Investigator even though the student may be called a PI.

Advisor Name (PRINT) and Signature

Date

Department Chair's Assurance Statement

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a

sponsoring company, patents, licensure) associated with this research project?
☐ Yes (provide a description of that interest in a separate letter addressed to the HIC.)
☐ No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?
☐ Yes (provide a description of that interest in a separate letter addressed to the HIC)
☐ No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

John Krystal MD _____ _____
Chair Name (PRINT) and Signature Date

Psychiatry _____
Department

YNHH Human Subjects Protection Administrator Assurance Statement

Required when the study is conducted solely at YNHH by YNHH health care providers.

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:
- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to notify the IRB if I am aware of any real or apparent institutional conflict of interest.
- The principal investigator of this study is qualified to serve as P.I. and has the support of the hospital for this research project.

_____ _____ _____
YNHH HSPA Name (PRINT) and Signature Date

SECTION V: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

Aim 1: To examine the feasibility to recruit, randomize, retain, and assess participants in a one-week exposure therapy combined with single dose ketamine infusion or a series of two ketamine infusions.
Aim 2: To demonstrate the beneficial effects of combining low dose ketamine (0.5 mg/kg or 0.2mg/kg infused over 40 min) and intensive prolonged exposure (PE) therapy on PTSD symptoms as assessed by structured interviews and behavioral ratings in the OIF/OEF/OND population.
Aim 3: To assess changes in the brain's functional connectivity and hyper-reactivity in the "mood" and "memory" network which include: the amygdala, striatum, insula, anterior cingulate cortex,

hippocampus and prefrontal cortex in pre and post treatment task listening to the trauma narrative/neutral narrative/and a significant non-traumatic memory narrative pre and post treatment. **Aim 4:** To demonstrate the ability of ketamine treatment to restore structural connectivity by using diffusion weighted imaging (DTI) and global probabilistic tractography with anatomical priors, we will estimate the cingulum fractional anisotropy (FA) at baseline, and post treatment.

2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Prolonged Exposure therapy (PE) is based upon the Emotional Processing Theory of PTSD, which emphasizes the critical importance of mentally processing traumatic memories in order to alleviate PTSD symptoms (Foa, Hembree, & Rothbaum, 2007). The content of the therapy itself emerged from exposure therapy, which has long been used to help anxious clients confront fear and anxiety-producing stimuli in a non-threatening environment. PE utilizes psychoeducation about anxiety and its treatment and breathing exercises to provide clients with some immediate anxiety-reducing skills (Foa, Rothbaum, Riggs, & Murdock, 1991). Among the techniques employed in PE, imaginal and in vivo exposure constitute the core of the therapy. Imaginal exposure asks clients to audibly recount a traumatic event while mentally visualizing the experience, and is typically repeated during therapy sessions. In vivo exposure involves the client repeatedly confronting avoided environments or stimuli in real life, and is often assigned as homework (Foa & Rothbaum, 1998). Imaginal exposure enhances memory reconsolidation of the traumatic memories, leading to reduction of re-experiencing symptoms, while in vivo exposure reduces avoidant behavior and exaggerated startle responses. By assisting the client to not engage in avoidance behavior during these exposures, the maladaptive associations between feared stimuli, avoidance behavior, and psychological relief become weakened as new, positive associations are forged. The client learns that memories of their trauma are not identical to the trauma itself, and as this occurs the ability of environmental, cognitive, and behavioral reminders of trauma to elicit a fear response is diminished.

PE is widely considered to be an efficacious and effective treatment for chronic PTSD (Eftekhari, Stines, & Zoellner, 2006; Foa et al., 1991; Foa et al., 2005). However, the therapy has limitations: it is traditionally administered on a weekly basis over a period of 3 or more months. Naturalistic studies suggest that more than 60% drop out of therapy before receiving appropriate dose to experience a significant symptoms reduction (Harpaz-Rotem & Rosenheck, 2011). Since PTSD is often exacerbated over time, faster treatment may also prevent the escalation of minor affective disturbances into chronic anxiety and depression symptoms, particularly when delivered temporally close to a traumatic event. A recent investigation of a novel, intensive form of PE delivered over 7 consecutive days found that PSTD clients were able to achieve outcomes comparable to traditional PE in a fraction of the time (Ehlers et al., 2014). Even among those receiving this intensive brief treatment, however, about 47% of clients did not demonstrate significant improvement as measured by the Clinician Administered PTSD Scale. Augmenting PE with pharmacotherapy has been suggested as a promising solution to address treatment-resistant PTSD (Eftekhari, Stines, & Zoellner, 2006). Case studies report that significant additional improvements have been observed made when PE was supplemented with SSRIs (Marshall, Carcamo, Blanco, &

Liebowitz, 2003) and with sertraline (Otto et al., 2004). However, rates of nonresponse to these pharmacological approaches remain high, indicating a tremendous need to test novel pharmacological approaches to PTSD.

The N-methyl-D-aspartate receptor (NMDAR) antagonist ketamine has been shown to have rapid-acting effects on treatment-resistant depression. Following a single 0.5mg/kg subanesthetic infusion of ketamine, numerous studies report antidepressant effects among 43%-90% of clients which present within 4 hours post-infusion and persist for 7-28 days (Ibrahim et al., 2012; Phelps, Brutsche, Moral, Luckenbaugh, Manji, & Zarate, 2009; aan het Rot et al., 2008; Zarate et al., 2006). Initial investigation of ketamine as a fast-acting treatment for PTSD has been met with positive empirical support: a randomized control trial found greater PTSD symptom reduction and lengthier symptom alleviation following a single infusion of ketamine compared to the active placebo midazolam (Feder et al., 2014).

Based on the current research findings on the therapeutic effectiveness of trauma focus psychotherapy and of ketamine, combining the two treatments may yield a promising new rapid 7-day treatment for PTSD. As PTSD symptoms' structure is comprised of several unique clusters which include re-experiencing, avoidance, numbing/depression and hypervigilance we hypothesize that by combining Ketamine with PE we can address these symptoms clusters more effectively. This treatment has the potential to produce a significant therapeutic effect that otherwise would take months to occur by tapping on the enhanced neuroplasticity and the antidepressant effect of ketamine (which lasts between 24hrs to 7 days), to promote rapid changes in learning and memory using prolonged exposure therapy within this unique "window of opportunity".

We will also use 3T MRI scanner to assess biomarkers of structural connectivity (using DTI) and fMRI for biomarkers of functional connectivity and hyper-reactivity to trauma reminders. DTI has been used to study PTSD, where connectivity deficits have been described in cortico-limbic structures that do not appear to be dependent upon a diagnosis of traumatic brain injury (Admon et al., 2013). PTSD is also associated with differences in activation or in functional connectivity in the amygdala, striatum, insula, anterior cingulate cortex, hippocampus and prefrontal cortex (Shin, L. & Liberzon, I., 2010). It was found that ketamine enhances functional connectivity at rest, but reduces working memory task-related activation and connectivity and the functional antagonism between the executive and default mode networks (Driesen N. et al., 2013). We propose to evaluate functional connectivity using f-MRI in the current study to test the following hypotheses: 1) Alterations in functional connectivity (hyperconnectivity of amygdala-insula-cingulate and reduced DLPFC-amygdala connectivity prior to treatment, will predict treatment response; and 2) Ketamine will normalize these changes to better understand this type of functional relationship between the PFC and amygdala. It is also important to link the connectivity changes in humans to alterations in brain activation during trauma cue exposure. Thus, we will also use personal trauma narratives during fMRI scans (from the PE) to assess level of brain activation during trauma reminders. Prior studies in PTSD have suggested that patterns of cortico-limbic functional connectivity are associated with circuit reactivity to traumatic reminders and anticipation of negative stimuli (Fonzo et al., 2010).

Using a biomarker-informed, double blind placebo-controlled design, the present proposal aims to examine the efficacy of a single dose or series of two doses of ketamine infusion, as compared to midazolam, that will be combined with an intensive one week PE, in producing a rapid and sustained reduction in PTSD symptomatology in veterans. In addition, we propose use of state-of-the-art neuroimaging assessments at baseline and at the end of treatment trial to gain insight into the neurobiology of PTSD and the neural mechanisms dictating treatment response or resistance.

References

Admon, R. et al. (2013). Stress-induced reduction in hippocampal volume and connectivity with the ventromedial prefrontal cortex are related to maladaptive responses to stressful military service. *Hum Brain Map, 34,* 2808-16.

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Foa, E. & Rothbaum, B. (1998). *Treating the trauma of rape: Cognitive-behavioral therapy for PTSD*. New York: Guilford Press.

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Phelps, L., Brutsche, N., Moral, J., Luckenbaugh, D., Manji, H., & Zarate, C. Jr. (2009). Family history of alcohol dependence and initial antidepressant response to an N-methyl-D-aspartate antagonist. *Biological Psychiatry 65*, 181–184.

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Shin, L. & Liberzon, I. (2010). The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology, 35*, 169-91

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3. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths**. Describe the setting in which the research will take place.

   Participants: Participants will be physically healthy adult males and females meeting the diagnostic criteria for PTSD, as well as the inclusion and exclusion criteria specific in the human subjects section.

Procedures: Potential subjects will be referred to the present study via the National Center for PTSD screening protocol (HSS# IHR009) which was approved by the West Haven VA IRB. Participants will be first interviewed over the phone to obtain information related to their eligibility, including a medical records review if available. As per the screening protocol, qualifying participants will then schedule an appointment to determine that they meet all of the inclusion and exclusion criteria. The initial psychological screening may take place remotely or in -person, as has been approved by the West Haven VA IRB. During their first screening appointment participants will complete:

***Screening Measures*:**
Assessments that will be used during the psychological evaluation are listed below.

Psychological Evaluation:

1. *Alcohol and Consumption Habits:* This is a brief measure that documents alcohol, caffeine, and nicotine habits.
2. *Brief TBI Screen:* The Brief Traumatic Brain Injury Screen, also called the DVBIC TBI Screening Tool, is a 3-item instrument used to evaluate the presence of head injury and related symptomatology.
3. *Mini-Mental State Examination (MMSE):* The MMSE measures the severity and progression of cognitive impairment, including functions such as registration, attention and calculation, recall, language, ability to follow simple commands and orientation.
4. *Columbia-Suicide Severity Rating Scale (C-SSRS):* The C-SSRS is a brief clinician administered and standardized measure that uniquely assesses essential information about suicide behavior, ideation, lethality and severity, and distinguishes between suicidal occurrences and non-suicidal self-injury.
5. *Early Trauma Inventory (ETI-SR):* The ETI-SR is a self-report instrument to assess childhood trauma and includes physical, emotional and sexual abuse as well as general traumas.
6. *Life Events Checklist (LEC):* The LEC is a self-report instrument that measures reports of traumatic life events.
7. *Massachusetts General Hospital Antidepressant Treatment History Questionnaire (MGH-ATRQ)*-This is a self-rated questionnaire used to determine treatment resistance in major depressive disorder.
8. *Penn State Worry Questionnaire (PSWQ):* The PSWQ is a self-report questionnaire to assess for 'worry' symptoms that are typical of generalized anxiety.
9. *Pittsburgh Sleep Quality Index (PSQI):* The PSQI is a self-report questionnaire to assess sleep quality and sleep disturbance.
10. *PTSD Checklist (PCL):* The PCL is used to measure PTSD symptoms and is a self-report questionnaire that has high reliability.
11. *Quick Inventory of Depressive Symptoms – Self-Report (QIDS-SR):* The QIDS-SR is a patient-rated depression instrument.
12. *Socio-demographic/General Information:* At intake, demographic data and medical history will be assessed with interviews and self-report forms that provide data on age, race, socioeconomic status, marital status, educational and occupational levels, and

significant medical history. These are adapted from previous diagnostic and clinical studies at this center.

13. *Structured Clinical Interview for DSM (SCID):* The SCID is the gold standard instrument for establishing a DSM diagnosis. It is a structured, clinician administered interview which aim to establish both current and lifetime psychiatric diagnoses record for each study participant.

Medical Assessments (conducted in-person only):

1. Physical exam by a licensed physician, or Advanced Practice Registered Nurses (APRN's).
2. Routine laboratory studies including a complete blood count (CBC) w/ differential, a comprehensive metabolic panel (e.g., BUN/creatinine, glucose, sodium, potassium, chloride, carbon dioxide, calcium, AST, ALT, fT4, TSH, bilirubin, total protein, VDRL, vitamin B12, folate, etc.), HCG, CRP, ESR, a complete lipid panel and electrolytes in addition to urinalysis and urine toxicology screen. Additional tests will be requested as clinically indicated.
3. Urine toxicology screens will be performed at the screening appointment and will be administered more frequently if the clinician or research staff becomes concerned about possible illicit drug use. Patients will be informed of random urine drug screens.
4. An EKG will be performed.
5. Pregnancy Tests- female subjects will have a blood sample drawn for a pregnancy test.
6. MRI safety form

If upon completion of these measures interested participants qualify for the current study, a member of the research team will be notified and contact the participant to schedule an initial visit for this Yale preformed study. Data from the screening protocol will be collected only after the participant has given a signature of informed consent to be involved in the current study.

Study Design: This is a biomarker-informed, double blind, active placebo-controlled design. The participants will be randomized based on a randomization table that will be available solely to the Yale Investigational Drug Service. Subjects will be stratified by gender and age. Participants will undergo 7 consecutive visits, and two follow-up visits.

Figure 1. Summary of Study Procedures for Single-infusion group

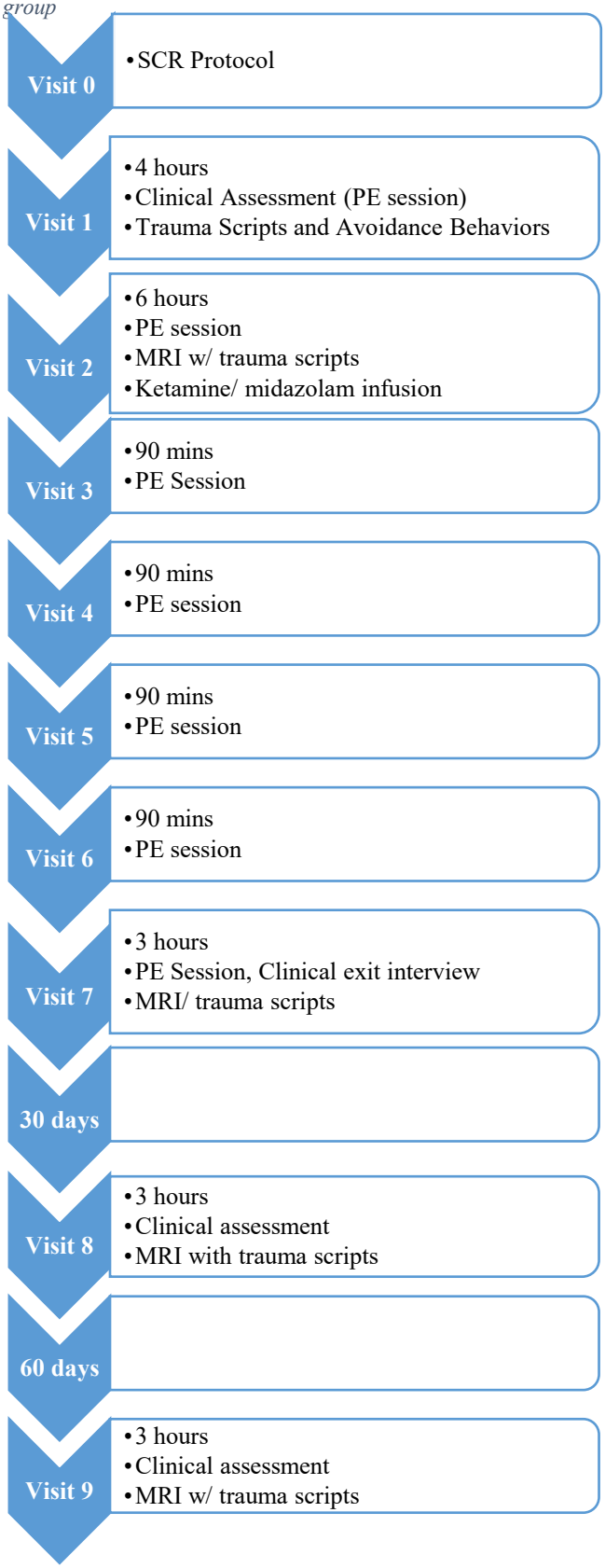
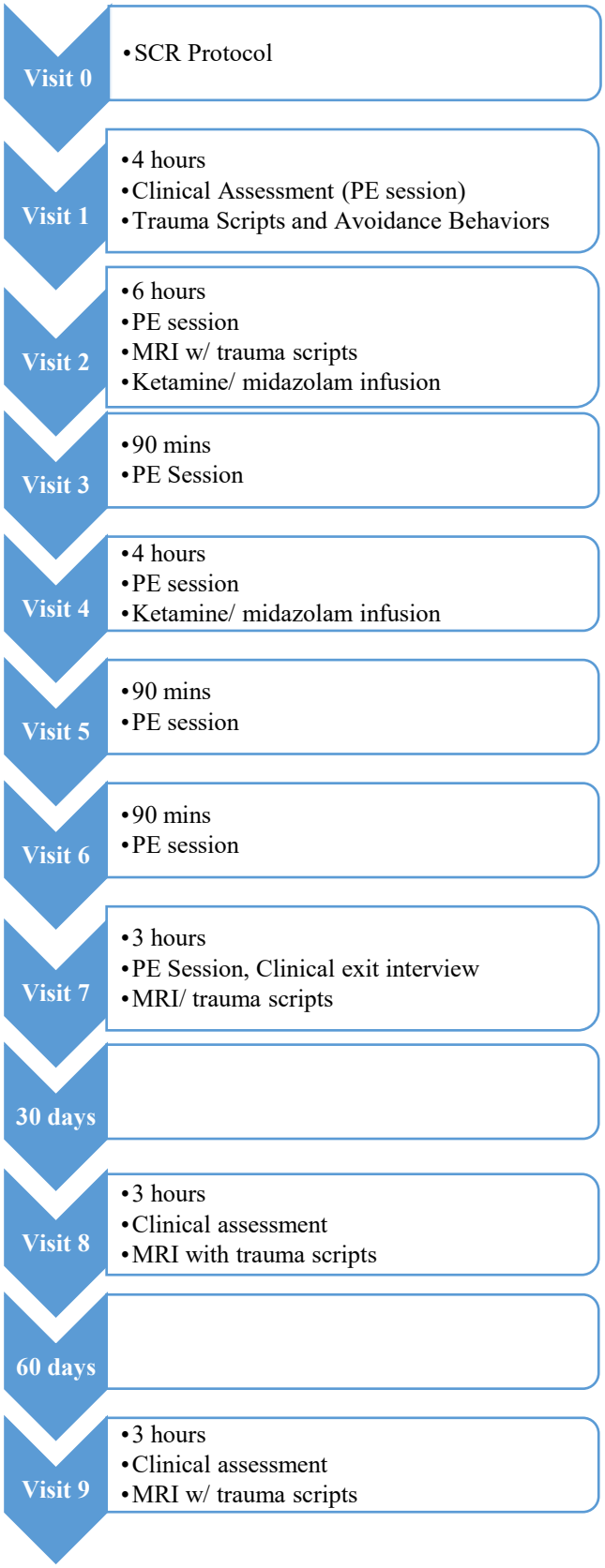


Figure 2. Summary of Study Procedures for 2-infusion group



Visit 1: At the initial visit the participant will first receive the fully informed consent process. Study procedures, risks, benefits, and withdrawal procedures will be explained and any questions will be answered by the appropriate study personnel. The subject will then be asked sign a consent form if they choose to participate. A trained clinician will administer the Clinical-Administered PTSD Scale for DSM-V (CAPS-5) to ensure that participants meet the diagnostic criteria for inclusion. At this time participants will also complete the State-Trait Anxiety Inventory (STAI), Beck Depression Inventory (BDI). The initial clinical assessment may take place remotely using Zoom, if it is not feasible for an in-person session to occur due to physical distance or risk of infection from COVID-19.

Eligible participants will be asked to describe specific life events: one traumatic, one sad, and one neutral.
Afterwards they will be asked to circle at least 3 physiological responses and to complete the Impact of Events Scale as it pertained to the experience they just described. Scripting of trauma memories is a reliable means for eliciting psychophysiological responses in PTSD that are prognostically predictive. The script development session may be conducted remotely for participants unable to attend an in-person session due to distance of COVID-19 related concerns. At this visit, participants may be asked to wear a portable physiotracking watch to record their GSR and Heart rate during trauma recall (E4 Wristband, Empatica Inc.)
We will examine those responses before and after ketamine infusion and PE therapy in order to establish the relationship between combined treatment with ketamine and intensive PE and objective measures of PTSD symptomatology.

After the session has ended, research staff will compose a written script for each experience incorporating 3 physiological responses—the script is portrayed in the 2nd person and present tense. The script is normally 30s-60s in length when read aloud and is narrated onto an audio file for use in later visits.

Eligible participants will be assigned to either one or two infusions of the investigative drug (ketamine) or the active placebo. Subjects assigned to receive one infusion will be randomized to receive either the standard (0.5mg/kg) or lowered (0.2mg/kg) dose. Thus the 5-arm design will include the following groups (1) PE + 0.5mg/kg single-infusion ketamine (2) PE + 0.2mg/kg single-infusion ketamine (3) PE + single-infusion of midazolam (4) PE + two 0.5mg/kg infusion ketamine and (5) PE + two-infusions of midazolam.

The first PE session will then occur. The focus of this session will be evaluation of traumatic life events, and the identification of 3-5 avoidance behaviors. These behaviors will serve as the focus of *in vivo* exposure exercises.

Visit 2:
The second visit will consist of (1) a PE session (2) MRI with trauma scripts and (3) infusion with ketamine or midazolam.

Participants will report to the TAC Center approximately 1 and a half hours before the scheduled scan time. They will meet the study PE therapist who will deliver the first PE therapy session in the exam room which is mainly psychoeducational, and will provide the participant with information about PTSD and the therapeutic process. This session will take about 30 min.

All subjects will be asked not to drink or eat the night before the scan and to drink plenty of fluids during the day before the scan. They will be given clear juice when they first arrive. Next, a YCCI nurse will place two IV lines: one for infusing saline or ketamine and another for blood samples. If we are unable to place two lines, we will run the protocol with one line and not draw blood samples, if necessary.

Participants will be scanned in one of the 3T Siemens Trio scanners, using a 64-channel receiver array head coil. After completing the MRI safety checklist, participants will have electrodes attached to measure Galvanic Skin Response (GSR) and heart rate. Participants will then be positioned in the scanner. Baseline GSR/ECG will first be measured while participants are listening to a 5-minute relaxation recording. Next, high-resolution, T1-weighted anatomical images will be collected for each subject using an MPRAGE sequence (TR=2.5 s, TE=3.93 ms, TI=900 ms, flip angle=80, 176 sagittal slices, 1x1x1 mm, 256x256 matrix in a 256 mm FOV). Functional data will then be collected using the MRRC multiband sequence (multiband factor=4, TR=1s, TE=30 ms, 60 near axial slices, 2x2x2 mm, 110x110 matrix in a 220x220 mm FOV) and local shimming to the field of view. During the first functional scan, headphones will play each of the participant's scripts from visit 1. The presentation order of the scripts (trauma, sad, neutral) will be randomized. Before listening to the script the participant will be instructed to remember the experience as vividly as possible while it plays (script listening). Each script (neutral, sad and trauma memory) will be played 3 times. Between scripts there will be 30-second periods of relaxation. In a second functional scan subjects will be asked to lie still with their eyes open (resting-state scan). An Eyelink eyetracker mounted in the MR machine will measure pupillometry during the scan. Finally, Diffusion tensor images (DTI) will be acquired, using the MRRC multiband sequence (multiband factor=4, 64 noncollinear directions with b-value = 1000 sec/mm2, plus an acquisition without diffusion weighting; TR = 2200 msec; TE = 84 msec; in-plane resolution: 2x2mm2 and 64 two-millimeter slices without gap).

Infusion Procedure

After the reactivation of the scripted memories will end, the ketamine/ midazolam infusion procedure will begin. The ketamine/midazolam infusion will occur inside the scanner at the MRRC.

Participants will be reminded that they are free to end the infusion at any time if they experience significant discomfort. A physician who is trained and has significant experience with both ketamine and infusion studies will oversee and administer the ketamine infusions. A nurse will accompany the subject throughout the study sessions, from the insertion of bilateral cannula for drug infusion and blood sampling, to the recovery following ketamine infusion. Whilst subjects undergo the infusion, their heart

rate and blood pressure will be closely monitored (approximately every 5 minutes). Participants in the single-infusion condition will receive a steady state ketamine infusion of 0.50 mg/kg or 0.2mg/kg. Participants in the two-infusion condition will receive a steady state ketamine infusion of 0.50 mg/kg. Midazolam infusions will take place over a similar time course at a rate 0.045 mg/kg, except for individuals aged over 60 who will receive 0.032 mg/kg over the same time course. The infusion will continue for 40 minutes. If the heart rate goes higher than 100 or the subject reports being lightheaded or dizzy, they will be medically evaluated as to whether they can safely continue the protocol. Participants will then undergo a full psychiatric interview, allowing us to rate, in detail, with standard psychiatric rating scales the nature and severity of any changes in their thoughts, emotions and perceptions that the infusion has induced. They will also rate their level of sedation, before, during and after scan.

Blood samples (7 cc each) will be taken 3 times equally spaced apart during the midazolam and ketamine infusions. These will be used to assess plasma ketamine levels. The samples will be stored at -80 degrees Celsius in the YCCI. Pulse, blood pressure, respiration, and oxygen saturation will be assessed before the ketamine and saline infusions and approximately every five minutes thereafter. After the ketamine infusion is finished, the subject will be placed at a recovery room to rest and the examiner will provide time for participants to discuss their experiences, have questions answered, and be observed for any untoward effects. However, the patient will not be informed of when they received ketamine. Intravenous catheters will be removed once the study doctor has determined that the patient is stable and sufficiently recovered from the effects of the ketamine. Participants will receive a light meal. To assure patient safety, they will not be discharged until they have modified Aldrete's score of 7 and no symptoms of orthostatic hypotension. In the period between the end of infusion and discharge, participant vital signs will be assessed approximately every 15 minutes. Participants will be counseled not to drive for 24 hours. They will be accompanied by a designated adult of their choice to take them to their residency or if they prefer will be placed in a Taxi by one of the study staff personnel to ensure their safe ride home.

Ketamine Experience Interview

Participants' experiences of the ketamine/midazolam infusion will be rated using standard psychiatric interview questionnaires including the Brief Psychiatric Rating Scale (BPRS), PANSS, the Paranoia inventory questionnaire (PIQ), the Clinician Administered Dissociative States Scale (CADSS) and the Rating Scale for Psychotic Symptoms (RSPS).

PE Session

After participants have recovered from the infusion, they will meet with the PE therapist for approximately 90 mins. Participants will receive PE therapy from a standardized manual delivered by a Dr, Harpaz-Rotem or any other trained clinician from the study team. The content of therapy will progress from basic psychoeducation to individualized imaginal exposure to the traumatic event and in vivo exposure to the situation the participants listed in session 1 that he wishes no longer to avoid and are safe. Participants will be asked to wear a portable GSR device while in the PE therapy sessions. In addition, the study therapist will assign homework exercises to complement the skills practiced in

session. PE is considered to be the most effective psychotherapy for PTSD and was tested in more than 50 clinical trials.

The total length of the second visit is 6 hours.

Visits 3-6:
Participants will report to the Decision Neuroscience Lab on the 8th floor of 300 George St. on days 3—6 of the study. The length of these sessions will be 90 minutes.

Participants who receive 2-infusions will also receive ketamine or midazolam infusions on day 4 of the experiment. For these participants, all the same infusions procedures described above (for infusion #1) will be repeated. The infusion will take place either inside the MRI machine at the MRRC. Participants will be monitored until the effects of ketamine have worn off, and study staff will ensure that either a taxi is provided, or a subject-designated adult driver will transport the participant home.

Visit 7:
A final session of PE therapy will be given. After this, participants will walk to TAC for a post-treatment MRI and fMRI. Procedures for the scan will match those of Visit 2. The trauma scripts will again be presented through headphones while the participant is undergoing scanning. No Ketamine/midazolam infusion will be given following the presentation of the scripts. Participants will complete the following end of treatment measures: PCL, BDI, STAI, C-SSRS and PSQI. Total visit time including MRI – 3 hours. Based on the final assessment, participants will be then be discharged from the clinical trial by the PI, as all treatment procedures have concluded.

Follow-up visits (Visits 8 & 9) to monitor potential long-term study benefits:
Participants will be asked to return to TAC approximately 30 days and 90 days after Visit 7 to assess the long-term psychiatric effects of the intervention. The study clinician will evaluate the mental health of the participant and ensure that no negative sequelae of the ketamine infusion persist. Participants will complete the PCL, BDI, STAI, C-SSRS and PSQI at this time. Following clinical assessment, participants will undergo MRI and fMRI while the original scripts are played through headphones. Procedures for the scan will be identical to those listed previously; no infusion will be given. The total length of time for each follow-up visit is 3 hours. If participants are unable to attend the follow-up scan sessions, the study clinician will conduct the ketamine follow-up evaluation via telephone. Additionally, the PCL, BDI, STAI, C-SSRS, and PSQI will be collected over telephone if the participant cannot attend the follow-up scans.

4. Genetic Testing N/A ☒

A. Describe

i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned

ii. the plan for the collection of material or the conditions under which material will be received
iii. the types of information about the donor/individual contributors that will be entered into a database
iv. the methods to uphold confidentiality

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects?
C. Is widespread sharing of materials planned?
D. When and under what conditions will materials be stripped of all identifiers?
E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?
    i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)?

F. Describe the provisions for protection of participant privacy
G. Describe the methods for the security of storage and sharing of materials

5. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

   For the current study, 120 participants (ages 21-70) meeting the diagnostic criteria for PTSD are needed to investigate the therapeutic potential of PE combined with ketamine infusion. An extensive medical and psychiatric assessment will be conducted to exclude subjects who are at increased risk.

   Females of childbearing potential will be eligible, and appropriate safeguards will be instituted, e.g. serum pregnancy test and reproductive counseling, to prevent pregnant patients from enrolling or subjects conceiving, respectively, during this investigation.

6. **Subject classification:** Check off all classifications of subjects that will be <u>specifically recruited for enrollment</u> in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐ Children	☐ Healthy	☐ Fetal material, placenta, or dead fetus
☐ Non-English Speaking	☐ Prisoners	☐ Economically disadvantaged persons
☐ Decisionally Impaired	☐ Employees	☐ Pregnant women and/or fetuses
☐ Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #4 for further requirements)

7. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

Inclusion Criteria:

- Male or female between the ages of 21-70 years. This age range was chosen to fit with prior samples in which no adverse effects of ketamine have been observed. Adults in the 18-20 ranges have been eliminated because previous experience indicates that they often lack the maturity to participate effectively in similar protocols. Females will be included if they are not pregnant and agreed to utilize a medically accepted birth control method (to include oral, injectable, or implant birth control, condom, diaphragm with spermicide, intrauterine device, tubal ligation, abstinence, or partner with vasectomy) or if post-menopausal for at least 1 year, or surgically sterile.
- Must not have a medical/neurological problem or use medication that would render ketamine unsafe by history or medical evaluation.
- Diagnosis of PTSD with a score of 25 or higher (i.e. severe PTSD) on the Clinician-Administered PTSD Scale (CAPS-5) at screening.
- Subjects on FDA-approved antidepressant, trazodone, atypical neuroleptic, prazosin, or clonidine may enter the study if they have been on a stable treatment, as determined by the study clinician, for at least 4 weeks prior to randomization. Following randomization, small changes to doses may be allowable at the PI's discretion.
- Able to provide written informed consent.
- Able to read and write English.

Exclusion Criteria:

- Patients with a diagnostic history of borderline personality disorder, obsessive compulsive disorder, schizophrenia or schizoaffective disorder or currently exhibiting psychotic features as determined by the Structured Clinical Interview for DSM (SCID) (First, et al. 2010); dementia or suspicion thereof, are excluded. Patients with history of bipolar disorder will be included only if they have not experienced a manic or hypomanic episode in the 30 days prior to enrollment. Other DSM Axis I disorders are permitted as long as they are not considered primary disorders.
- Patients with a history of antidepressant-induced hypomania or mania as determined by open-ended psychiatric interview.
- Current, ongoing serious suicidal risk as assessed by evaluating investigator or by scoring 5 or more on item-10 of the MADRS.
- Moderate severity or greater Substance Use Disorder (excepting Alcohol Use Disorder) during the 3 months prior to randomization, as determined by the SCID. Alcohol Use Disorder may be allowed based on the judgment of study physician/APRN/clinician that patients can remain sober for all study visits.
- Subjects on a prohibited medication (see Table 1). Patients will not be taken off medication for the purpose of this study.
- 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.

- Positive pregnancy test at screening or prior to any study drug infusion.
- Breathalyzer showing an alcohol level > 0% at screening, or at the discretion of the investigator, prior to any study drug infusion.
- Resting blood pressure lower than 90/60 or higher than 150/90, or resting heart rate lower than 45/min or higher than 100/min.
- Any significant history of serious medical or neurological illness.
- Any signs of major medical or neurological illness on examination or as a result of ECG screening or laboratory studies.
- Abnormality on physical examination. A subject with a clinical abnormality may be included only if the study physician considers the abnormality will not introduce additional risk factors and will not interfere with the study procedure.
- A positive pre-study (screening) urine drug screen or, at the study physician's discretion on any drug screens given before the scans.
- Pregnant or lactating women or a positive urine pregnancy test for women of child-bearing potential at screening or prior to any imaging day.
- Any history indicating learning disability, mental retardation, or attention deficit disorder.
- Known sensitivity to ketamine.
- Body circumference of 52 inches or greater.
- Body weight of 250 pounds or greater.
- History of claustrophobia.
- Presence of cardiac pacemaker or other electronic device or ferromagnetic metal foreign bodies in vulnerable positions as assessed by a standard pre-MRI screening questionnaire.
- Donation of blood in excess of 500 mL within 56 days prior to dosing.
- History of sensitivity to heparin or heparin-induced thrombocytopenia.

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.

- .

8. How will **eligibility** be determined, and by whom?

   Eligibility will be determined by the PI and/or the study physicians. Additionally, participants recruited from local clinics will have eligibility determination made by the PIs listed in the research staff section. Eligibility determinations will be made using the listed inclusion and exclusion criteria.

9. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

   Ketamine administration

   Ketamine is a dissociative anesthetic that has been used clinically since the late 1960s (Domino, Chodoff, & Corssen, 1965). Despite extensive experience, there is no clear and compelling evidence of long-term toxicity associated with ketamine administration in medically supervised settings (Perry et al., 2007a; Schorn & Witwam, 1980). However, there are acute medical and neuropsychiatric sequelae that deserve special consideration. The ketamine doses employed in the Healthy group 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. Some subjects may experience heightened PTSD reactions. Additionally, vivid dreams and poor sleep quality after infusion of ketamine have also been reported, although dream content was not necessarily unusual and alterations in sleep were not reported on subsequent nights.

   The doses used in this protocol produce blood levels that are 1/6 to 1/3 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 [109]. Adverse events included nausea and

vomiting, sedation, anxiety, hypotension, insomnia and nightmares and transient pain in the infusion arm.

Phlebotomy

We may need to draw additional blood for the routine laboratory testing. Inserting a needle into a vein is safe when done by professionals under clean conditions. Sometimes a bruise will occur at the puncture site and on rare occasions a blood clot or an infection may form in the vein. If this occurs, appropriate treatment will be instituted immediately.

Risks associated with blood loss are minimal. Less than 200 cc will be drawn, and this represents 40% of a 500-cc blood donation.

Psychiatric Evaluation and Clinical Assessments

These are all non-invasive, should add no risk, and 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. Only subjects' code numbers will be recorded on the forms themselves to protect confidentiality.

Magnetic Resonance Imaging (MRI)

Magnetic resonance (MR) is a technique that uses magnetism and radio waves to take pictures and measure chemicals of various parts of the body. The United States Food and Drug Administration (FDA) has set guidelines for magnet strength and exposure to radio waves, and we will carefully observe those guidelines.

Some people may feel uncomfortable or anxious. As previously noted, some subjects may experience heightened PTSD reactions while in the scanner. If this happens, the subject may ask to stop the study at any time, and we will take them out of the MR scanner. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste or feel tingling sensations or muscle twitches. These sensations usually go away quickly but subjects will be encouraged to tell the research staff if they have them.

There are some risks with an MR study for certain people. If the subject has a pacemaker or some metal objects inside their body, they may not be in this study.

Another risk is the possibility of metal objects being pulled into the magnet and hitting the subject. This MR study is for research purposes only and is not in any way a clinical examination. The scans performed in this study are not designed to find abnormalities. The primary investigator, the lab, the MR technologist, and the Magnetic Resonance Research Center are not qualified to interpret the MR scans and are not responsible for providing a diagnostic evaluation of the images. If a worrisome finding is seen on a scan, a radiologist or another physician will be asked to review the relevant images. Based on his or her recommendation (if any), the primary investigator or consulting physician will contact the

subject, inform them of the finding, and recommend that they seek medical advice as a precautionary measure. The decision for additional examination or treatment would lie solely with the subject and their physician. The investigators, the consulting physician, the Magnetic Resonance Research Center, and Yale University are not responsible for any examination or treatment that subjects receive based on these findings. The images that will be collected in this study are not a clinical MR exam and for that reason, they will not be made available for diagnostic purposes.

Portable Physiotracker

It is possible that some individuals experience skin irritation as a result of wearing the portable physiotracker device. In such cases subjects will be advised to discontinue wearing the device.

10. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

Recruitment and Informed Consent

Prior to enrollment, subjects will have face-to-face or virtual interviews with one of the investigators where the nature of the project, the risks, the benefits, and the alternatives to participation in the project will be discussed with the subject and, if necessary, the subject's family. A focused history will be taken, and a checklist of hazards will be reviewed with the subject. If, following these discussions, the subject continues to be interested in the project, informed written consent will be obtained on the consent form approved by the Yale University Human Investigation Committee (HIC). Thereafter, the project investigators assume clinical responsibility for the care of the subject.

General risk-minimizing strategies:

1. Effective screening to exclude subjects who would be placed at a greater risk. This includes a comprehensive psychiatric and medical evaluation, physical examination, and the screening studies. Trained staff, under the supervision of the PI, will conduct all screening procedures.

2. The investigator or a designated person will explain the benefits and risks of participation in the study to each subject. Subjects will be asked to verbalize their understanding of all aspects of the consent, including risks, benefit and alternatives. The voluntary nature of research studies is always emphasized.

3. To reduce the risk of metal objects being pulled into the magnet and hitting the subject we will require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. We will also ask all people involved with the study to walk through a detector designed to detect metal objects. No metal will be allowed to be brought into the magnet room at any time. Once the subject is in the magnet, the door to the room will be closed so that no one from outside accidentally goes near the magnet.

Each subject will fill in the MR safety sheet prior to participation in the fMRI study. We will stress to subjects that we want them to read and answer the questions very carefully and to tell us any information they think might be important.

All research staff that might accompany the subject into the magnet room will undergo annual MR safety training and will also fill out the MR safety sheet each year.

The subject will be watched closely throughout the MR study. Subjects will be monitored by an MR operator in respect to all aspects pertaining to the MR scan, and the research team that is comprised of a physician, a nurse, and a research scientist. Subjects may ask to stop the study at any time and we will take them out of the scanner.

4. All subject information will be kept confidential and only members of the investigative team with appropriate IRB/HIC and HIPAA training will have access to the study data. Data will be maintained and secured in locked file cabinets or password protected electronic media. A numbering code will be used to assign a unique identifier to each subject.

5. A Data and Safety Monitoring Plan is described below.

All personnel are trained in an established procedure for terminating the infusion and dealing with emergency. There will be an M.D. present at all times who will be able to perform immediate resuscitation in the unlikely event it is needed.

Subject Monitoring and Emergency Procedures

An experienced clinical research team will closely monitor the subjects. All of the information obtained from subjects participating in this study will be coded by numbers and kept in locked files in the research unit to ensure confidentiality. One member of the two to three-person team will watch the subjects while in the magnet room. Visual and verbal contact will be maintained throughout the infusion. Subjects who become claustrophobic in the magnet will be removed immediately from the magnet room. Subjects who experience distress during the infusion for any reason, including seizures, loss of consciousness or pain will have the infusion terminated immediately. All team members will be thoroughly familiar with the established emergency plan. If immediate resuscitation is needed the physician present during the study will perform this procedure.

Anxiousness

If a subject is anxious and expresses a desire to end the infusion then the study will be immediately terminated.

Irritation

If there is irritation due to IV blood sampling, the physician present during the study will examine the subject, and the study will be terminated if the subject is in pain. If skin irritation is caused by the portable physiotracker, its use will be discontinued.

Effects of ketamine

Before participating, healthy subjects undergo careful psychiatric and medical evaluation. A research nurse, study physician and research scientist will be present in the MRRC magnet suite **at all times** during test sessions to provide support and consistent "reality testing" for individuals experiencing confusion or transient psychosis. If a subject report that symptoms cannot be tolerated, the ketamine infusion will be stopped immediately.

Subjects will be observed for at least 4 hours after the termination of testing, and if intolerable physical or behavioral symptoms persist, subjects will be admitted to the Clinical Neuroscience Research Unit at the Connecticut Mental Health Center for further observation and overnight if necessary. Participants will be informed that they may not drive or operate machinery for 24 hours after 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. Subjects will be provided a number to call to reach an on-call research psychiatrist (24 hours/day) should unpleasant effects occur after subjects have left the testing facility. Medication effects will be reviewed and "debriefed" with subjects following each test day by a study clinician. If necessary, subjects will be administered oral diazepam to reduce residual symptoms and their participation in the study will be terminated if necessary. Such subjects will be monitored as found appropriate by the study physicians.

We are also taking a number of precautions to help reduce the chance of having an unpleasant response to ketamine or to reduce the severity of any lingering medication effects. These precautions include:

1) A research clinician and research nurse and research scientist will be present throughout the study, at all times, to offer support and to help clarify the progress of the test day in case the medication causes feelings of confusion.
2) Medications are available (Valium) to relieve distress related to the behavioral effects of ketamine.
3) We will ask the subject to remain in the recovery room for several hours after the behavioral effects of ketamine should have worn off.
4) We will review the test day with the subject to deal with your feelings and reactions to each test day before you leave.
5) We will ask the subject to contact us at any time if any unpleasant effects occur.
6) We will ask the subject not to engage in demanding work in the day following the test sessions and we will work with the subject to schedule your test days accordingly.
7) If the subject has any lingering medication effects, such as sedation, we will terminate the remaining test days and work with him/her until these side effects have resolved.
8) If the subject develops psychiatric symptoms, we may admit him/her to the hospital. This may be involuntary if he/her are in danger of harming yourself or others.
9) We will also contact the subject at 24 hours, one week, and one month after the last infusion for safety reasons

If inpatient psychiatric admission is clinically indicated, subjects may be admitted to the inpatient Clinical Neuroscience Research Unit (CNRU) at Connecticut Mental Health Center

(CMHC) for closer supervision free of charge. Subjects will then be discharged with appropriate follow-up care when their proximal safety risk is minimal.

11. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.

    a. What is the investigator's assessment of the overall risk level for subjects participating in this study?

    We have assessed the proposed study as one of moderate risk. We do not view the risks associated with ketamine as minimal. We do not view the risks associated with the combined use of ketamine and ^{13}C-MRS imaging as minimal. Given the now established safety and validity of the current research of ketamine in our prior work, we do not view the proposed study as high risk. However, 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.

    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study?
    Not Applicable

    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://www.yale.edu/hrpp/forms-templates/biomedical.html for
        i. Minimal risk
        ii. Greater than minimal

    Adverse events will be monitored for each subject participating in the study and attributed to the study procedures /design by one of the study physicians together with the principal-investigator, Ilan Harpaz-Rotem, Ph.D., according to the following categories:
    a.) Definite: Adverse event is clearly related to investigational procedures(s)/agent(s).
    b.) Probable: Adverse event is likely related to investigational procedures(s)/agent(s).
    c.) Possible: Adverse event may be related to investigational procedures(s)/agent(s).
    d.) Unlikely: Adverse event is likely not to be related to the investigational procedures(s)/agent(s).
    e.) Unrelated: Adverse event is clearly not related to investigational procedures(s)/agent(s).

    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
2. Moderate adverse event
3. Severe

Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events:

In addition to grading the adverse event, one of the study physicians together with the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it:

- is life-threatening
- results in in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- results in a congenital anomaly or birth defect OR
- results in death
- 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
- 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 HIC or HSC is necessary.

Plan for reporting serious and unanticipated and related adverse events, anticipated adverse events occurring at a greater frequency than expected, and other unanticipated problems involving risks to subjects or others to the HIC

The investigator will report the following types of adverse events to the HIC:
a) serious and unanticipated and possibly, probably or definitely related events;
b) anticipated adverse events occurring with a greater frequency than expected;
c) other unanticipated problems involving risks to subjects or others.
These adverse events or unanticipated problems involving risks to subjects or others will be reported to the HIC or HSC within 48 hours of it becoming known to the investigator, using the appropriate forms found on the website.

Plan for reporting adverse events to co-investigators on the study, funding and regulatory agencies

For the current study, the following individuals, funding, and/or regulatory agencies will be notified:
□ All Co-Investigators listed on the protocol.
□ National Institutes of Health

One of the study physicians together with the principal investigator, will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

d. For multi-site studies for which the Yale PI serves as the lead investigator: N/A
   i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed?
   ii. What provisions are in place for management of interim results?
   iii. What will the multi-site process be for protocol modifications?

12. **Statistical Considerations:** Describe the statistical analyses that support the study design.

A mixed effects regression model will reveal a significant group by time interaction, with rapid reduction in PTSD symptoms in the ketamine group compared to midazolam.

SECTION VI: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, state N/A and delete the rest of the section.

A. DRUGS, BIOLOGICS and RADIOTRACERS

1. **Identification of Drug, Biologic or Radiotracer:** What is (are) the **name(s)** of the drug(s) biologic(s) or radiotracer(s) being used? Identify whether FDA approval has been granted and for what indication(s).

Ketamine has U.S. Food and Drug Administration (USFDA) approval as the only anesthetic for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketamine is also indicated for anesthesia induction prior to the administration of other general anesthetic agents or to augment low potency anesthetics such as nitrous oxide.

Midazolam is a short-acting benzodiazepine central nervous system (CNS) depressant.
It also has U.S. Food and Drug Administration (USFDA) approval for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 12 years of age and older.

All protocols which utilize a drug, biologic or radiotracer **not** approved by, but regulated by, the FDA, or a radiotracer regulated by the RDRC, must provide the following information:

a. What is the Investigational New Drug (IND) **number** assigned by the FDA?
   Not Applicable

b. Who holds the IND?
Not Applicable

c. All protocols which utilize a radiotracer not approved by, but regulated by the FDA must provide the IND number: _____N/A_____
Alternatively, use of the investigational radiotracer may be under RDRC/RSC oversight: (check if appropriate)_____N/A____

For all investigational radiotracers, attach a copy of the RDRC/RSC application (for radioisotopes used in the PET Center, PET Center personnel may complete this step)
Go to http://rsc.med.yale.edu/login.asp?url=myApps.asp. When you have logged in, complete the application and attach a copy to this submission.

Alternatively, an **exemption from IND filing requirements** may be sought for a clinical investigation of a drug product that is lawfully marketed in the United States. If there is no IND and an exemption is being sought, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

Exempt Category 1
The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:

i. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug. ☒ Yes ☐ No
ii. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product. ☒ Yes ☐ No
iii. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. ☒ Yes ☐ No
iv. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56). ☒ Yes ☐ No
v. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs. ☒ Yes ☐ No

Exempt Category 2 (all items i, ii, and iii must be checked to grant a category 2 exemption)

☐ i. The clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following (check all that apply):
☐ Blood grouping serum
☐ Reagent red blood cells
☐ Anti-human globulin

☐ ii. The diagnostic test is intended to be used in a diagnostic procedure that confirms the

diagnosis made by another, medically established, diagnostic product or procedure; and

☐ iii. The diagnostic test is shipped in compliance with 21 CFR §312.160.

Exempt Category 3

☐ The drug is intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.60

Exempt Category 4

☐ A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

Ketamine has been administered to over 10,000 patients and reported in greater than 100 individual research investigations, including many (as previously cited) from our department. 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). In healthy subjects, the typical subanesthetic doses used are about 0.23 mg/kg bolus of over 1 minute followed by 0.58 mg/kg/hour infusion (e.g. Refs (Anand et al., 2000; D'Souza, Singh, Elander, Carbuto, Pittman, de Haes, et al., 2012; Gunduz-Bruce et al., 2011; Krystal et al., 1999; Krystal et al., 1998; Krystal et al., 2005). Extensive experience suggests that ketamine administration is not associated with long-term toxicity. The doses of ketamine administered produce blood levels 1/3 - 1/6 those associated with blood levels achieved when ketamine is used as a primary surgical anesthetic. Since 1989, studies at our department administered ketamine on over 800 occasions to over 300 subjects. Our group has extensive experience using ketamine in psychiatric research.

In addition to the recently found rapid-acting antidepressant effect, ketamine has been extensively used in human research as a model of psychosis owing to its acute psychotomimetic and cognitive adverse effects (Kantrowitz & Javitt, 2010). In healthy volunteers, subanesthetic doses of ketamine induce transient perceptual disturbances, dissociative experiences, cognitive dysfunction, affective changes, thought disorder, and mild physical symptoms (Bubenikova-Valesova, Horacek, Vrajova, & Hoschl, 2008). These studies showed dose-dependent effects with increased symptoms at higher doses (Krystal et al., 1994b; Newcomer et al., 1999; Oye, Paulsen, & Maurset, 1992). However, the symptoms were transient, starting within minutes of ketamine infusion and lasting up to 2 hours (Krystal et al., 1994b). Recently, Perry and colleagues at Yale reviewed a dataset of 450 healthy subjects who collectively received a total of 833 ketamine infusions in a medically supervised setting as part of laboratory studies (Perry et al., 2007a). This report noticed no evidence of serious

adverse events, residual sequelae, or sensitization. Only 2% of subjects experienced non-serious adverse reactions. These emerging side effects resolved by the end of the test day in all subjects, except for one participant who experienced symptoms for 4 days (Perry et al., 2007a).

3. **Source:** a) Identify the source of the drug or biologic to be used.

   Ketamine and midazolam will be acquired from the research pharmacy of either the Connecticut Mental Health Center (CMHC) or YNHH IDS

   b) Is the drug provided free of charge to subjects? ☒ Yes ☐ No
   If yes, by whom?

   Drugs will be administered during Day 2 for all participants, and also on Day 4 for those in the 2-infusion groups. A physician and a nurse from the research team will administer the drug as described in the methods.

4. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.
   Check applicable Investigational Drug Service utilized:

   ☒ **YNHH IDS**
   ☒ **CMHC Pharmacy**
   ☐ **PET Center**
   ☐ **Other:**
   ☐ **Yale Cancer Center**
   ☐ **West Haven VA**
   ☐ **None**

   Note: If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.

5. **Use of Placebo:** ☐ **Not applicable to this research project**
   If use of a placebo is planned, provide a justification which addresses the following:
   a. Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this.

      An active placebo will be used for this trial. There are no alternative pharmacotherapies to midazolam. The midazolam will generate some level of sedation so that participants would not know if they were in the treatment group (Ketamine) or the placebo. It has a rapid onset of action, high effectiveness, and low toxicity level. The alternative is to not take the drug.

   b. State the maximum total length of time a participant may receive placebo while on the study.

      Infusion with ketamine or midazolam will occur once during the study for those in the single-infusion groups, and 2 times for those in the two-infusion groups. Each infusion will occur over a period of about 45 minutes.

   c. Address the greatest potential harm that may come to a participant as a result of receiving

placebo.

Midazolam is a benzodiazepine that may result in side effects including drowsiness, confusion, amnesia, ataxia, and hang-over like symptoms. However, midazolam is typically safe and effective for most individuals when infused at the rates specified for the current study (Riss, Colyd, Gates, & Collins, 2008).

d. Describe the procedures that are in place to safeguard participants receiving placebo.

Participants will be supervised at all times during infusion with midazolam by a trained doctor and nurse practitioner experienced in infusion procedures. As described in the Minimizing Risk section, several precautions are in placed to ensure participant safety, including:

- Consistent "reality testing" for individuals experiencing confusion or transient psychosis.
- If a subject report that symptoms cannot be tolerated, the infusion will be stopped immediately.
- Subjects will be observed for at least an hour after infusion ends and will be admitted to the Clinical Neuroscience Research Unit at the Connecticut Mental Health Center for further observation if necessary.
- Participants will be informed that they may not drive or operate machinery for 24 hours after 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.
- Subjects will be provided a number to call to reach an on-call research psychiatrist (24 hours/day) should unpleasant effects occur after subjects have left the testing facility.
- If necessary, subjects will be administered oral diazepam to reduce residual symptoms and their participation in the study will be terminated if necessary.

6. **Use of Controlled Substances:**
Will this research project involve the use of controlled substances in human subjects?
☒ Yes ☐ No *See HIC Application Instructions to view controlled substance listings*.

If yes, is the use of the controlled substance considered:
☒ Therapeutic: The use of the controlled substance, within the context of the research, has the potential to benefit the research participant.
☐ Non-Therapeutic: *Note, the use of a controlled substance in a non-therapeutic research study involving human subjects may require that the investigator obtain a Laboratory Research License. Examples include controlled substances used for basic imaging, observation or biochemical studies or other non-therapeutic purposes. See Instructions for further information.*

7. **Continuation of Drug Therapy After Study Closure** ☐ **Not applicable to this project**

Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

☐ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access.

☒ No If no, explain why this is acceptable.
Ketamine/ midazolam will be administered to participants during the study, followed by an intensive dose of psychotherapy. Ketamine is predicted to enhance the learning that takes place during psychotherapy, but is not currently indicated as a long-term pharmacotherapy.

B. DEVICES

2. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☒No *If Yes, please be aware of the following requirements*:

a. A YNHH New Product/Trial Request Form must be completed via EPIC: **Pull down the Tools tab in the EPIC Banner, Click on Lawson, Click on "Add new" under the New Technology Request Summary and fill out the forms requested including the "Initial Request Form," "Clinical Evidence Summary, " and attach any other pertinent documents. Then select "save and submit" to submit your request**; and

b. Your request must be reviewed and approved **in writing** by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

2. What is the name of the device to be studied in this protocol?

Has this device been FDA approved? ☐ Yes ☐ No
If yes, state for what indication.

3. **Background Information:** Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.

4. **Source:**
   a) Identify the source of the device to be used.

   b) Is the device provided free of charge to subjects? ☐ Yes ☐ No

5. What is the PI's assessment of risk level (significant or non-significant) associated with the use of the device?

☐ **Significant Risk (SR) Device Study:** A study of a device that presents a potential for serious risk to the health, safety, or welfare of a participant and 1) is intended as an implant; 2) is used in supporting or sustaining human life; or otherwise prevents impairment of human health; 3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or 4) otherwise presents a potential for serious risk to the health, safety, or welfare of a participant.

Significant Risk Devices require an Investigational Device Exemption (IDE) issued by the FDA.

What is the **IDE number** assigned by the FDA?

Did the FDA approve this IDE as **Category A** (experimental/investigational) or as **Category B** (non-experimental/investigational)?

Who holds the IDE?

☐ **Non-Significant Risk (NSR) Device Study:** A study of a device that does not meet the definition for a significant risk device and does not present a potential for serious risk to the health, safety, or welfare of participants. Note that if the HIC concurs with this determination, an IDE is not required.

6. **Abbreviated IDE or Exempt IDE:** There are abbreviated requirements for an IDE and there also are exemptions to the requirement for an IDE. *See the criteria in the HIC Application Instructions,* Section VI.B.4 at http://www.yale.edu/hrpp/resources/docs/100FR1aHICProtocol_Application_Instructions5-25-11.pdf *to determine if these pertain to this study.*

☐ **Abbreviated IDE or Exempt IDE** – *If criteria set forth in the HIC Application Instructions are met, copy and paste the completed relevant section from the Instructions into this application.*

7. **Investigational device accountability**:
   a. State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. **Targeted Enrollment: Give the number of subjects:**
   a. targeted for enrollment at Yale for this protocol: 120
   b. If this is a multi-site study, give the total number of subjects targeted across all sites___

2. **Indicate recruitment methods below.** Attach copies of any recruitment materials that will be used.

☒ Flyers ☒ Internet/Web Postings ☒ Radio

☒ Posters
☐ Letter
☐ Medical Record Review
☒ Departmental/Center Newsletters
☒ YCCI Recruitment database
☐ Other (describe):

☐ Mass E-mail Solicitation
☒ Departmental/Center Website
☐ Departmental/Center Research Boards
☒ Web-Based Clinical Trial Registries
☒ Clinicaltrials.gov Registry (do not send materials to HIC)

☐ Telephone
☐ Television
☒ Newspaper

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.
Subjects will be recruited by flyers, public advertisements (newspaper, radio, internet posting) by word of mouth, clinician referral, contact with community service groups and clinics (VA PTSD clinics-West Haven and the Newington mental health clinic, CMHC, Yale Depression Research Program, the Yale Psychiatric Research Hospital, and the YCCI recruitment database). We may also utilize the National Center for PTSD newsletter to advertise the study and the trial will be registered at Clinical Trials.gov. Subjects will be identified by their response to advertisements and/or internal recruiting.

b. Describe how potential subjects are contacted.

The subjects will be asked to call us if they are interested in participating in the research study. There will not be any web based questionnaires utilized for pre-screening subjects in this study.

c. Who is recruiting potential subjects?

All listed member of the research team and the NCPTSD screening protocol staff may recruit potential participants. The aforementioned clinics may also refer potentially eligible clients to the study.

4. Screening Procedures

a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☒ Yes ☐ No
b. If yes, identify below all health information to be collected as part of screening and check off any of the following HIPAA identifiers to be collected and retained by the research team during this screening process.

HEALTH INFORMATION TO BE COLLECTED:
Current psychiatric treatment
Current medications
Allergies

HIPAA identifiers:
☒ Names
☒ All geographic subdivisions smaller than a State, including: street address, city, county, precinct, zip codes and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly-available data from the Bureau of the Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains

more than 20,000 people, and (2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
☒ Telephone numbers
☐ Fax numbers
☒ E-mail addresses
☐ Social Security numbers
☐ Medical record numbers
☐ Health plan beneficiary numbers
☐ Account numbers
☒ All elements of dates for dates related to an individual, including: birth date, admission date, discharge date, date of death, all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older
☐ Certificate/license numbers
☐ Vehicle identifiers and serial numbers, including license plate numbers
☐ Device identifiers and serial numbers
☐ Web Universal Resource Locators (URLs)
☐ Internet Protocol (IP) address numbers
☐ Biometric identifiers, including finger and voice prints
☐ Full face photographic images and any comparable images
☐ Any other unique identifying numbers, characteristics, or codes

5. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐ Yes, all subjects
☐ Yes, some of the subjects
☒ No

If yes, describe the nature of this relationship.

6. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study
☒ For recruitment purposes only
☐ For inclusion of non-English speaking subject if short form is being used

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data;

Initial screening procedures occurring over the phone with subjects does not allow for signed authorization to occur. However, potential subjects will be told that their information will be recorded during the call to determine if they are eligible to participate in the study. Subjects will be verbally asked if they agree to this process and if they are, the screening will occur. The initial clinical interview session may take place over Zoom if it is not feasible for subjects to attend an in-person session due to physical distance or risk of infection due to COVID-19.

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data;

In order to determine if a subject is eligible to come into the clinic for a screening visit, we conduct phone screens. We ask their permission to record data and tell them that everything we write down is confidential and will be kept in a locked cabinet. Therefore, due to prescreening on the phone, we cannot get their signed authorization. We can only get their verbal authorization.

By signing this protocol application, the investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

7. **Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:
   ☒ Compound Consent and Authorization form
   ☐ HIPAA Research Authorization Form

8. **Consent Personnel:** List the names of all members of the research team who will be obtaining consent/assent.
   Listed in IRES IRB

9. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

   If an individual appears to meet enrollment criteria and is interested in participating, a face-to-face interview, or Zoom or telephone call is conducted at by one of the project investigators. 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. 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. When it is not feasible for written consent to be obtained in person due to physical distance or threat of infection due to COVID-19, a consent will be emailed from a Yale account to the subject, who will then sign and return the document.

If the individual remains 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 YNNH, YCCI, CMHC, the VACHS, or to receive treatment on a private basis from a referring clinician.

10. E**valuation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

After trained and knowledgeable research personnel explain all aspects of the research protocol with a consent form at hand, the potential subject will be asked to communicate a reciprocal understanding of the protocol. This "say back" method has demonstrated reliability among educators in ascertaining degree of comprehension.

11. Documentation of Consent/Assent: Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

Research personnel capable of determining consent will conduct this process with the most up-to-date copies of the Yale informed consent documentations at hand.

12. Non-English-Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

Not applicable as non-English speaking subjects will not be enrolled.

12(a) As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment?
YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are found on our website at: http://www.yale.edu/hrpp/forms-templates/biomedical.html. If the translation of the short

form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via amendment prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

13. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐ **Not Requesting a consent waiver**
☒ **Requesting a waiver of signed consent**
☐ **Requesting a full waiver of consent**

A. Waiver of **signed** consent: (Verbal consent from subjects will be obtained. **If PHI is collected, information in this section must match Section VII, Question 6**)

☒ **Requesting a waiver of signed consent for Recruitment/Screening only**

If requesting a waiver of signed consent, please address the following:
a. Would the signed consent form be the only record linking the subject and the research?
☐ Yes ☐ No
b. Does a breach of confidentiality constitute the principal risk to subjects?
☐ Yes ☐ No

OR

c. Does the research activity pose greater than minimal risk?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☒ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☒ No

☐ **Requesting a waiver of signed consent for the Entire Study (**Note that an information sheet may be required.)

If requesting a waiver of signed consent, please address the following:
a. Would the signed consent form be the only record linking the subject and the research?
☐ Yes ☐ No
b. Does a breach of confidentiality constitute the principal risk to subjects?
☐ Yes ☐ No

OR

c. Does the research pose greater than minimal risk? ☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** ☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

B. **Full waiver** of consent: (No consent from subjects will be obtained for the activity.)

☐ **Requesting a waiver of consent for Recruitment/Screening only**

a. Does the research activity pose greater than minimal risk to subjects?

☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity

☐ No

b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No

c. Why would the research be impracticable to conduct without the waiver?

d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

☐ **Requesting a full waiver of consent for the Entire Study (Note: If PHI is collected, information here must match Section VII, question 6.)**

If requesting a full waiver of consent, please address the following:

a. Does the research pose greater than minimal risk to subjects?

☐ Yes ***If you answered yes, stop. A waiver cannot be granted.***

☐ No

b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No

c. Why would the research be impracticable to conduct without the waiver?

d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

SECTION VIII: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

a. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

Names
Home addresses
Telephone Numbers
Email addresses
All elements of dates for dates related to an individual, including: birth date, admission date, discharge date, date of death, all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older

b. How will the research data be collected, recorded and stored?

Research personnel will collect research data via direct interview after potential subjects sign release of information for available informants. This data will be recorded in both written and/or electronic formats, and all confidential PHI will be quoted by number and stored in locked and secured files to ensure confidentiality

All confidential protected health information (PHI) obtained from screened and enrolled research subjects will be assigned a number and stored in locked and secured clinic repository to ensure confidentiality. This data will only be made available to the investigators and other research personnel, the National Institutes of Mental Health (NIMH) and Yale's HIC. Additional confidentiality measures follow the procedures and policies of CMHC and Yale.

c. How will the digital data be stored? ☐ CD ☐ DVD ☐ Flash Drive ☒ Portable Hard Drive ☒ Secured Server ☒ Laptop Computer ☒ Desktop Computer ☐ Other

d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

Do all portable devices contain encryption software? ☒ Yes ☐ No

All written confidential PHI will be quoted by number and stored in locked and secured locations at both sites to ensure confidentiality. All electronic PHI/PI resources will be encrypted and password-protected to preclude access by non-research personnel.

If no, see http://hipaa.yale.edu/guidance/policy.html

e. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

All electronic PHI (ePHI) will continue to be encrypted and password-protected after subject participation. Both written and ePHI will be destroyed 10 years after the protocol is completed.

f. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)

All research personnel listed on this protocol and Yale HIC will have access to written and ePHI and study data throughout and after the completion of the study until the data is destroyed at the discretion of the primary investigators. The Brain and Behavior Research Foundation, the funding source for this study, will also have access to subjects' PHI.

g. If appropriate, has a Certificate of Confidentiality been obtained? Yes

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h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview -incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported.

SECTION IX: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

The present study may benefit participants directly via infusion with ketamine followed by an intensive form of PE therapy. The combined treatment with ketamine and PE is predicted to help participants by reducing PTSD symptoms such as hyperarousal, re-experiencing trauma, and maladaptive avoidance behaviors. Results from the current study may provide clinicians with a novel evidence-based intervention option for treatment-resistant PTSD.

The relative risks and inconveniences associated with participation in this study, including ketamine administration, are balanced by the potential benefits to participants and society at large.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

   Not to participate

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

   Compensation for study procedures will break down as follows:

   Single-Infusion Group:

   Screening Clinic (Visit 0) ……..$50.00 for psychological assessment;
   $50.00 for medical assessment
   Visit 2 (first MRI)..…….……...$50.00
   Visit 2 (1st infusion)…….$100.00
   Visit 7 (second MRI)…….……...$150.00
   Visit 8 (one month follow-up)..……..$200.00
   Visit 9 (3-month follow-up)..……..$250.00
   Total ……..…… $850.00

Two-Infusion Group:

Screening Clinic (Visit 0) ……..$50.00 for psychological assessment;
$50.00 for medical assessment
Visit 2 (first MRI)..…….……...$50.00
Visit 2 (1st infusion)…….$100.00
Visit 4 (2nd infusion)……$100.00
Visit 7 (second MRI)…….……...$150.00
Visit 8 (one month follow-up)..……..$200.00
Visit 9 (3-month follow-up).……..$250.00
Total ……..…… $950.00

Subjects will receive payment for the screening procedures from the VA Screening protocol. Subjects will receive payments for Visits 2 -9 either by cash or via a Bank of America pre-paid debit card. The subject's name, address, and telephone number will be shared with Bank of America for ePayments. After the second payment milestone (second study visit) subjects will receive a card in the mail which will need to be activated over the phone. Subsequent milestones payments will occur after Visit 8 and again after Visit 9 and will automatically add additional funds to the subject's card.

At the principal investigator's discretion, only reasonable expenses, such as transportation costs to and from study locations will also be covered by the National Center for PTSD or by Yale Department of Psychiatry paying subjects with cash at the end of each study visit. Should any participants require local accommodations, a hotel room in New Haven will be provided by the National Center for PTSD or by Yale Department of Psychiatry. If too much time passes between the screening visit and first scan, it may be necessary for subjects to repeat the psychological interview, medical evaluation, or both. Subjects will be paid $50 for completing a repeat psychological screening session, and $50 for completing a repeat medical evaluation. If subjects come to the session but are unable to take part in the scheduled scans due to MRI downtime or scheduling error, a $50 show-up fee will be offered.

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

All services and evaluations are provided free of charge.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.
   a. Will medical treatment be available if research-related injury occurs? Yes
   b. Where and from whom may treatment be obtained? From the PI or an appropriate referral
   c. Are there any limits to the treatment being provided? Only that is limited by the subject ability to pay for the costs of the care provided
   d. Who will pay for this treatment? The subject and/or the subject's insurance

e. How will the medical treatment be accessed by subjects? Via the PI, the Connecticut Mental Health Center (CMHC), or emergency room visit

Medical treatment will be offered to the subjects for any physical injuries that they receive as a result of participating in this research. However, the subject or his/her insurance company is responsible for the cost. As required by Federal regulations, all subjects will be told that if they are physically injured, no additional financial compensation is available.