Title Research Project: **Ketamine Infusion for Social Anxiety Disorder**

Principal Investigator: Michael H. Bloch, MD

HIC# 1310012947

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HIC 1310012947

YALEUNIVERSITY
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Biomedical Research
100 FR1(2013-1)

Please refer to the HIC website for application instructions and information required to complete this application. The Instructions are available at http://www.yale.edu/hrpp/forms-templates/biomedical.html Submit the original application and one (1) copy of all materials including relevant sections of the grant which funds this project (if applicable) to the HIC.	**HIC OFFICE USE ONLY**	

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: Ketamine Infusion for Social Anxiety Disorder			
Principal Investigator: Michael H. Bloch, MD		**Yale Academic Appointment:** Assistant Professor in the Yale Child Study Center	
Department: Yale Child Study Center			
Campus Address: CNRU at CMHC, Yale University School of Medicine, 34 Park Street, New Haven, CT 06519			
Campus Phone: 203-974-7071	**Fax:** 203-785-7611	**Pager:**	**E-mail:**Michael.bloch@yale.edu
Protocol Correspondent Name & Address (*if different than PI*): Jerome Taylor, MD, Fellow Yale Child Study Center, 333 Cedar Street, New Haven CT 06510			
Campus Phone:785-2516, 785-7094	**Fax:**785-7400	**E-mail:**Jerome.taylor@yale.edu; Alt #: 203-589-0132	
YaleCancerCenter 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)X**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 projector 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
o 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?
o 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 con-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: Yale Child Study Center

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.
☐ VeteransAffairsHospital, 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 HavenVA HSS Approval Date:
☐ *Radioactive Drug Research Committee (RDRC) Approval Date:
☐ YNHH-Radiation Safety Committee (YNHH-RSC) Approval Date:
☐ Magnetic ResonanceResearchCenter PRC (MRRC-PRC) Approval Date:
☐ 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. 4 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: Epidemiologic and Behavioral
☐ Translational Research #1 ("Bench-to-Bedside")
☐ Translational Research #2 ("Bedside-to-Community")
☐ Clinical Research: Outcomes and 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.aspxor 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 a service or procedure that will be ordered, performed or result in charging in EPIC for individuals who are enrolled in a clinical research study, regardless if the charge is intended to be paid by the subject/their insurance or the research study.

Yes ☐ No☒

If you answered "yes", this study will need to be set up in OnCore Support
http://medicine.yale.edu/ymg/systems/ppm/index.aspx

8..Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ___ No _X__*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?
b.Will you be using any new equipment or equipment that you have not used in the past for this procedure?

c. Will a novel approach using existing equipment be applied?

If you answered "no" to question 7a, or "yes" to question 7b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

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
Michael H. Bloch, MD	Ketamine Infusion for Social Anxiety Disorder	Patterson Trust Award	☐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 ☐OtherFor 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: N/A

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.**

	Name	**Affiliation: Yale/Other Institution (Identify)**	**NetID**
Principal Investigator	Michael H. Bloch, MD	Yale Faculty at the Child Study Center ; Clinical Neuroscience Research Unit (CNRU) at CMHC	Mhb32
Role: Co-Investigator	Jerome H. Taylor Jr, MD	Yale Fellow in Adult and Child Psychiatry	Jht28

Role: Co-Investigator	Angeli Landeros-Weisenberger, MD	Yale Child Study Center	Al495
Role: Co-Investigator	Christopher Pittenger, MD	CMHC, Psychiatry	Pitt

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 Universityand 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-NewHavenHospital, 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.

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.

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.

_____ _____

Chair Name (PRINT) and Signature Date

_____

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

For HIC Use Only

_____ _____

Date Approved **Human Investigation Committee Signature**

This protocol is valid through _____

SECTION V: RESEARCH PLAN

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

To determine the short-term efficacy of ketamine compared to placebo in the treatment of severe social anxiety disorder (SAD). We will conduct a crossover trial in which 18 patients with severe SAD will be given a single infusion of ketamine or saline (placebo) and their SAD symptoms will be followed over a two week period. We will require 4 weeks between infusion doses in order to minimize carryover effects. Our primary outcome will be average improvement during the first 3 days following infusion on the Visual Analog Scale (VAS) of Anxiety States.

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.

- Social Anxiety Disorder is common and causes significant impairment.
- First-line treatments for Social Anxiety Disorder are only partially effective. Many SAD patients experience little or inadequate symptom relief with available treatments.
- Ketamine is a potent NMDA receptor antagonist. Ketamine represents an agent with a potentially novel mechanism of action for the treatment of anxiety disorders.
- Ketamine has demonstrated efficacy in the treatment of psychiatric disorders closely related to Social Anxiety Disorder including Major Depression, Bipolar Depression and possibly Obsessive-Compulsive Disorder.

Social anxiety disorder (SAD) affects approximately 12.1% of all Americans and is defined as a "marked and persistent fear of one or more social situations," causing impairment and distress(Kessler, Peters et al. 2005). SAD typically impairs academic achievement, work productivity, social relationships, and results in a significantly poorer quality of life (Lipsitz and Schneier 2000). SAD is associated with subsequent development of depression, alcoholism, and cardiovascular disease (Kessler 2003, Kessler, Peters et al. 2005).

Roughly one-third to one-half of patients with generalized SAD do not experience significant clinical benefit from current evidence-based treatment for SAD such as pharmacotherapy with selective serotonin reuptake inhibitors (SSRI) or venlafaxine and cognitive behavioral therapy (CBT) (Blomhoff, Spetalen et al. 2001, Davidson 2004, Baldwin, Anderson et al. 2005, Baldwin and Nair 2005). Failure of anxiety relief in patients with SAD is a source of substantial morbidity, distress, and decreases in quality of life. Novel pharmacological treatments are needed to improve patient outcomes with SAD.

Converging lines of evidence from neuroimaging and pharmacological studies support the importance of glutamate abnormalities in the pathogenesis of SAD. In a Magnetic Resonance Spectroscopy (MRS) study, an elevated glutamate to creatinine ratio was found in the anterior cingulate cortex of SAD patients when compared to healthy controls (Phan, Fitzgerald et al. 2005). Elevated thalamic glutamine levels have been demonstrated in patients with SAD (Pollack, Jensen et al. 2008). Pre-clinical rodent studies have also established a strong link between glutamate regulation and anxiety (Linden 2002, Walker and Davis 2002, Bergink, van Megen et al. 2004, Johnson, Inderbitzen-Nolan et al. 2005).

Ketamine is a potent antagonist of the N-methyl-D-aspartate (NMDA) receptor, a major type of glutamate receptor in the brain. Ketamine is routinely used for anesthetic induction because of its dissociative properties. However in research studies, ketamine is effective treatment in reducing symptoms in depressive and possibly anxiety disorders. In multiple controlled clinical studies, ketamine has produced a rapid antidepressant effect in unipolar and bipolar depression(Berman, Cappiello et al. 2000, Zarate, Singh et al. 2006, Maeng and Zarate 2007, Murrough, Perez et al. 2011, Valentine, Mason et al. 2011). Ketamine's anti-depressant effects peak 1-3 days following infusion. Ketamine's antidepressant effect is observed long after ketamine has been metabolized and excreted by the body and after ketamine's sedative and dissociative effects have dissipated (Figure 1-3).

Figure 1: RM Berman et al (2000)

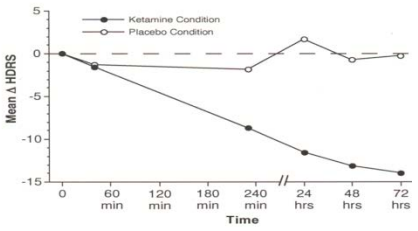


Figure 2: CA Zarate et al (2006)

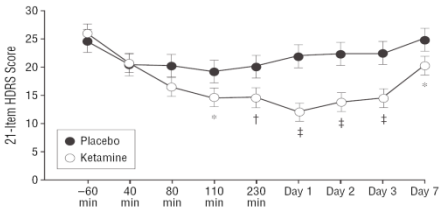
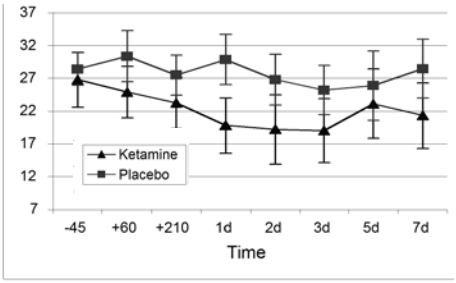


Figure 3: GW Valentine et al (2011)



The results of several clinical studies suggest that ketamine may also have significant anxiolytic effects. Patients with major depressive disorder given a single ketamine infusion have shown strong and significant reductions in comorbid anxiety symptoms. A trial including 11 depressed patients demonstrated a significant reduction in anxiety symptoms (Hamilton Anxiety Rating Scale (HAM-A)) following ketamine infusion (mean HAM-A pretreatment score 23.4 ± 6.5; mean HAM-A score after 230 minutes 14.3 ± 7.8; $t(9) = 3.39$, $p < .01$, Effect Size=1.4)(Salvadore, Cornwell et al. 2009). This improvement is supported by one of the earlier placebo-controlled trials of ketamine which demonstrated that the psychic anxiety item was one of 4 (out of 21) items on the HAM-D demonstrating significant improvement after ketamine infusion (Hofmann, Newman et al. 1995, Zarate, Singh et al. 2006). We propose a randomized, placebo-controlled crossover study to explore the efficacy and time course of action of intravenous ketamine in the treatment of SAD.

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.

- We propose a crossover trial in which 18 adults with severe SAD will be given a single infusion of ketamine or saline (placebo) and their SAD symptoms will be followed over a two week period.
- We will require at least a 4-week interval between infusions in order to minimize carryover effects.
- An 18 subject crossover trial will give us sufficient power to demonstrate a significant effect of ketamine (compared to placebo) if the symptom improvement is comparable to that observed in Major Depressive Disorder.

Overview:
We propose a double-blind, placebo-controlled crossover trial to study the effects of intravenous ketamine for the treatment of SAD. All patients will be offered the option of at least one first line treatment (an SSRI, SNRI, or CBT) prior to study enrollment.
We will perform the first blinded infusion (ketamine or saline) on the first study day. The second blinded infusion (ketamine or saline) will be administered 28 days after the initial infusion. The study investigators will be blinded to the order of infusion which will be determined offsite by the Connecticut Mental Health Center (CMHC) Investigational Drug Service. The infusions will occur on the Clinical Neuroscience Research Unit (CNRU). Patients will be followed with clinical ratings and behavioral assessments for 2 weeks following each infusion. Clinical ratings (excluding the infusion day) will take place at a separate location (the Yale Child Study Center) by a rater unaware of clinical and side-effect ratings on the day of infusion. The side-effects and psychotomimetic ratings for ketamine will be performed by a separate rater, than the ratings of anxiety and depression. We chose this design because the psychometric and physiologic side-effects of ketamine often lead to unblinding and because the beneficial effects of ketamine have lasted for 3 weeks in depression, making the carry-over effects in shorter-duration crossover studies problematic.

Table 1. Assessments

	Screening	**Day 0 - First Infusion (Ketamine or Saline) and Day 0+28- Second Infusion (Ketamine or Saline)**					**Day 1 and Day 1+28**	**Day 2 and Day 2+28**	**Day 3 and Day 3+28**	**Day 5 and Day 5+28**	**Day 7 and Day 7+28**	**Day 10 and Day 10+28**	**Day 14 and Day 14+28**
		-1 hour	0 hour	1 hour	2 hour	3 hour							
INTERVENTION													
Infusion			X										
BAT													
Impromptu Speech*		X					X				X		

MEDICAL ASSESSMENT													
Vital Signs	X	X	X	X	X	X							
Physical Exam	X	X				X							
EKG	X	X				X							
Blood Tests	X												
Urine Tests	X	X											
CLINICAL RATINGS													
SCID	X												
LSAS	X	X				X	X	X	X	X	X	X	X
SDS	X	X				X	X	X	X	X	X	X	X
VAS**	X	X		X	X	X	X	X	X	X	X	X	X
ASI		X											
SSPS**		X					X				X		
PANAS**		X					X				X		
BAI**	X	X				X	X	X	X	X	X	X	X
HAM-D	X	X				X	X	X	X	X	X	X	X
STAI**	X	X				X	X				X		X
CGI	X	X				X	X				X		X
OE		X											
TE						X	X				X		
MMSE	X	X		X	X	X	X						
BPRS-PS	X	X		X	X	X	X						
CADSS	X	X		X	X	X	X						

*All ratings and tests are assessed before the impromptu speech on the behavioral assessment test (BAT) days

**These ratings are assessed both before and after the impromptu speech on the behavioral assessment test (BAT) days

Table 1 presents the overall design of this study in terms of interventions, clinical ratings, behavioral assessments and laboratory examinations. A baseline screening assessment to determine study eligibility, clinical ratings, and physical health will be conducted at least one week prior to study enrollment. On the first study day, the patients will receive an infusion of ketamine or placebo, and the second infusion will be performed on day 28. A battery of clinical and cognitive rating scales will be employed to determine the effects of ketamine administration on mood, anxiety, perceptual distortions, and cognitive function for the first 3 hours and first 14 days following the placebo and ketamine infusion period. Twenty-eight days will separate the first and second infusions.

Medical Assessments

During the screening visit, vital signs, physical exam, and clinical laboratory tests (i.e. CBC with differential, complete metabolic panel (CMP) (including electrolytes, LFTs, BUN, creatinine and glucose), TFTs, urine drug screen, and routine urinalysis) will be completed. A pregnancy test will be given to all females enrolled in the study prior to participating in the study sessions. Only the subject will be told the results of this testing. A total of 30 cc of blood will be drawn at this visit. In addition, an EKG will be performed and read in order to rule out any cardiac abnormalities. If the urine drug screen or the pregnancy test is positive, the subject will not be able to participate in the protocol.

Patients

18 SAD patients will be recruited through the Yale Center for Anxiety and Mood Disorders, local providers, social anxiety groups, flyers around the New Haven area, Clinicaltrials.gov, YCCI

sponsored events and recruitment database, and anxiety-related events in the area. (See below for inclusion criteria).

Intervention

Ketamine Administration: Following an overnight fast, ketamine 0.5 mg/kg (or saline) will be administered over a 40 minute period. Ketamine administration will be performed on the Clinical Neuroscience Research Unit. A research nurse and physician will be present at all times during the procedure. Ketamine has been studied in over 10,000 patients in more than 100 separate studies. Ketamine has a wide therapeutic window, and is usually given in doses of 1mg/kg – 4.5mg/kg IV over 60 seconds when used as a sole anesthetic agent. Ketamine side effects include elevated blood pressure and disorientation, among others. Our institution has had experience using ketamine safely in research studies involving psychiatric patients for the last 15 years.

The most common side effects of ketamine are (1) Elevated blood pressure, breathing rate and pulse rate, (2) Local pain at injection site and temporary rash and (3) A variety of temporary psychological symptoms including, but not limited to anxiety, sadness, disorientation, insomnia, flashbacks, hallucinations, and psychotic-like symptoms. These types of reactions have occurred in approximately 12% of patients given higher doses of ketamine when used for anesthesia. These symptoms usually last no more than a few hours. The most serious possible side effects of ketamine use are (1) Substance abuse/dependence, (2) Elevations in intraocular pressure that could lead to vision problems, (3) Allergic reaction and (4) Elevation in blood pressure that could result in stroke, heart problems and death. All the serious possible side effects of ketamine are rare. As a precaution all patients will be administered ketamine and monitored at the Clinical Neuroscience Research Unit for 3 hours following ketamine infusions. If the side-effects do not dissipate we will additionally offer patients hospitalization at Connecticut Mental Health Center for psychiatric side-effects or YNHH for medical side-effects.

Assessments

The rating scales utilized in the trial are detailed in the table below. Ratings 1-14 days post infusion will be conducted by raters that are blinded to treatment assignment and will not be present or have access to the data collected on the initial infusion day. All rating scales documenting the psychotomimetic side effects of ketamine (BPRS and CADSS) will be performed by a separate rater who is blinded to treatment assignment but was present at the initial infusion. All ratings and assessments will be performed by trained research staff.

The SCID (Structured Clinical Interview for DSM disorders) on the screening day may take up to 2 hours with complex patients. All other assessments combined will likely take less than 3 hours on assessment days. Of note, “Day 0” will likely require a full 8-hour day because patients receive the infusion and receive assessments before and after the infusion. On Day 0, food after the infusion will be provided at CMHC.

RATING SCALES:

1) *Liebowitz Social Anxiety Scale (LSAS)*: The LSAS is a standardized rating scale that assesses SAD severity (Liebowitz 1987).
2) *Visual Analog Scale (VAS) of Anxiety States:* The VAS includes scales for anxiety, drowsiness, high, irritability, anger, and sadness. These scales are 100 mm lines marked by participants at a point corresponding to the apparent intensity of the feeling state (0=none, to 100=most ever) (Aitken 1969).
3) *Self-Statement During Public Speaking Scale (SSPS):* The SSPS is a rating scale used to measure cognitions that occurred during a speech (Hofmann and Dibartolo 2000).
4) *Beck Anxiety Inventory (BAI*): The BAI is a standardized rating scale of anxiety severity (Beck, Epstein et al. 1988).
5) *Hamilton Depression Rating Scale (HAM-D):* The HAM-D is a standardized rating scale of depression severity (Williams 1988).
6) *Anxiety Sensitivity Index (ASI):* The ASI is a standardized rating scale of anxiety severity (Reiss, Peterson et al. 1986).
7) *State-Trait Anxiety Inventory (STAI):* The STAI is a standardized rating scale of trait and state anxiety (Spielberger 1983).
8) *Positive and Negative Affect Schedule (PANAS):* The PANAS is a rating scale of positive and negative affect (Watson, Clark et al. 1988).
9) *Clinical Global Impressions (CGI):* The CGI is a widely used instrument which assesses overall severity of illness and symptom improvement on 7 point scales. (Guy 1976).
10) *Brief Psychiatric Rating Scale, Positive Symptom Subscale (BPRS-PS):* The BPRS contains subscales assessing symptom and behavior clusters. We will only be using the positive symptoms subscale portion of the BPRS, which examines thought content, conceptual disorganization, hallucinatory behavior, and grandiosity(Overall and Gorham 1962, Shafer 2005).
11) *Clinician-Administered Dissociative States Scale (CADSS):* CADSS has self and interviewer administered items and evaluates aspects of dissociative symptoms.(Bremner, Krystal et al. 1998).
12) Outcome expectancy (OE) – The outcome expectancy will measure whether patients believe the treatment will be effective.
13) Sheehan Disability Scale (SDS) – The SDS is a rating scale that measures functional impairment due to anxiety (Sheehan 1983)
14) Treatment Evaluation (TE) – We will ask participants whether they believe they have received ketamine or placebo.

Impromptu Speech Behavioral Assessment Test

In addition to rating scales, the impromptu speech BAT will be used to assess SAD symptoms (Beidel, Turner et al. 1985, Hofmann, Newman et al. 1995, Ries, McNeil et al. 1998). Participants will be asked to speak about pre-determined topics for 10 minutes to a small audience of research staff (Beidel, Turner et al. 1985). Patients with more severe social anxiety symptoms are often not able to speak for the full 10 minutes and have shorter speech lengths when compared to those with less severe social anxiety symptoms (Beidel, Turner et al. 1985, Hofmann, Newman et al. 1995, Ries, McNeil et al. 1998). Furthermore, VAS-anxiety, BAI, STAI, PANAS, and SSPS will be assessed before and after the speech. Participants will also be asked to rate on a scale of 1-100 how well they think they will perform/performed on the speech. The speeches will be videotaped.

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.

Adults ages 18-65 with SAD with or without co-morbid MDD will be recruited through the Yale Anxiety and Mood Disorders clinic in the Yale University Psychology Department, local providers, social anxiety groups, flyers around the New Haven area, Clinicaltrials.gov, YCCI sponsored events and recruitment database, and anxiety-related events in the area.

PATIENTS WITH SOCIAL ANXIETY DISORDER:

Inclusion Criteria:

1) Male or female (post-menopausal, surgically sterile, or negative pregnancy test at screening and agreement to utilize an established birth control including complete abstinence during the testing period) between the age of 18 and 65 yrs.
2) Meet DSM-5 criteria for social anxiety disorder by structured clinical interview (SCID) and have a LSAS score >60. No current diagnosis of a psychotic disorder.
3) Psychiatrically stable. Patients must have had stable doses of all psychiatric medications for the month prior to treatment prior to study enrollment. If a patient has just begun taking an SSRI or SNRI, the patient must be taking the medication for at least 2 months prior to starting the study and it must be at least 1 month since SSRI dose change. Patients cannot receive CBT while in the study.
4) Medically and neurologically healthy on the basis of physical examination, CMP (including LFT's), TFT's,, CBC w/ diff, urinalysis, urine toxicology, EKG, and medical history. Individuals with stable medical problems that do not have CNS effects or interfere with medications administered (e.g., oral hypoglycemics) may be included if their medications have not been adjusted in the month prior to entry.
5) Patients abusing cocaine, opiates, and PCP will be excluded from the study. A urine toxicology screen will be used to ensure these substances are not being abused prior to study enrollment.
6) Able to provide written informed consent according to the Yale Human Investigation Committee (HIC) guidelines in English.

6. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment 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)

A pregnancy test will be administered to all females of childbearing potential. This result must be negative before enrolling in the study.

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

See inclusion criteria in table above.

Exclusion Criteria:
1. Positive pregnancy test
2. History of substance abuse disorder (cocaine, opiates, PCP) within the last 6 months or positive urine toxicology on screening (within the previous 6 months).
3. History of pervasive developmental disorder or psychotic disorder by DSM-IV-TR criteria
4. Medical comorbidity that significantly increases the risks associated with ketamine infusion (e.g. untreated hypertension, significant cardiovascular disease, glaucoma)

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

Screening: After an initial telephone contact to rule out obvious exclusions from the study protocol, potential participants will be scheduled for a screening visit at the Yale Child Study Center. A member of our research team will discuss all aspects of this research: its purpose, the procedures that will be performed, any/all risks of the procedures, possible benefits, and possible alternative treatments..All patients will also be informed that the standard of care for patients with SAD who have failed the first line treatments (SSRI, SNRI (or alternative SSRI), and CBT) is a trial of a monoamine oxidase inhibitor (MAOI), not ketamine (National Institute for Health and Care Excellence2013). The research team will discuss the inclusion and exclusion criteria for the study. If patients are considered eligible according to their diagnosis of SAD with disabling symptoms with or without comorbid MDD based on the SCID, Liebowitz Social Anxiety Scale

(LSAS) > 60 (Liebowitz 1987), and if they agree to enroll in the study, they will sign the consent forms and schedule a time to go to the CNRU for screening visit 2.

Screening visit 2 will occur on the CNRU (may be done directly after Screening Visit 1 if convenient for the participant), and medical assessments (physical exam, EKG, blood draw, and urinalysis), and a battery of psychological rating scales will be performed, as indicated in Table1 (excluding the SCID which is done during screening visit 1). We will also contact the subject's primary care provider or treating provider to confirm their psychiatric history and SAD diagnosis after receiving a signed release form from the subject.

Participants will be enrolled if a clinical diagnosis of generalized social anxiety disorder, meeting DSM-V criteria as determined by the Structured Clinical Interview for DSM-V – Patient Edition (SCID-P). All participants in our study will identify formal public speaking as one of their social fears. Additional diagnostic, demographic, and clinical data, including course of illness, education level, history of formal and public speaking, history of suicidal ideation and attempts, treatment history, and family psychiatric history, will be obtained by direct clinical interview. All such data will be formally recorded on the CNRU Patient Profile and entered into a computer.

Participants will be excluded from the study if they present with major active suicidal ideation, a history of serious medical or neurological illness, current psychoactive substance dependence (with the exception of marijuana, caffeine, and nicotine), mental disorders due to identified medical conditions, or non-affective psychotic disorder. Participants will also be excluded if they manifest signs of major medical or neurological illness on examination or as detected by laboratory studies. The routine laboratory studies will include a CMP (including LFT's), TFTs, , CBC w/ diff, urinalysis, urine toxicology, EKG, and medical history, and a urine pregnancy test for females. Care will be taken to exclude pregnant women. Female participants will have a serum pregnancy test prior to receiving any treatment or testing in the study and will be informed of the importance of not becoming pregnant during the study. Participants will be excluded if they are judged to be so clinically unstable that participation in the study might represent a significant clinical risk or are unwilling to stay on a stable medication regimen for the length of this study.

After lab results are received and if the patient remains eligible as indicated by meeting the inclusion criteria, the patient will be called in order to schedule their first infusion. In the case of abnormal test results, the proper referrals will be made to ensure the patients receive the appropriate clinical care.

Eligibility will be **determined by** the PI and co-investigators based on the study inclusion criteria (above).

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 medication approved by the Food and Drug Administration to be used as an anesthetic. It is a dissociative anesthetic that has been used in humans since the late 1960's. Despite extensive experience there is no clear evidence of long-

term toxicity associated with ketamine administration. However the acute behavioral side effects of this medication warrant particular attention. Krystal et al, administered ketamine to healthy subjects at the West Haven VAMC(Krystal, Karper et al. 1994). The study showed that ketamine produces dose-related effects at sub-anesthetic effects in healthy subjects. At 0.1 mg/kg administered over 40 minutes, the low dose in the VA protocol, ketamine produced little more than a tingling in the extremities and a "little buzzing in the head". At 0.5 mg/kg, the VA study's high dose, and the dose proposed in this protocol, ketamine transiently elicited both the positive and negative symptoms of schizophrenia, dissociative symptoms, attentional impairments, a preferential impairment in delayed over immediate recall, increased perseverative errors on the Wisconsin card sort test, and decreased verbal fluency. In the sub-anesthetic dose utilized in this study, perceptual changes dissipate within 10-20 minutes following the termination of ketamine infusion. Ketamine also increased prolactin and cortisol, while blunting a test day decline in plasma HVA. Ketamine increased systolic and diastolic blood pressure by approximately 10-15 mm Hg, without a clear effect on pulse. Ketamine did not produce gross disorientation, as evidenced by complete absence of an effect on the MMSE and the successful completion of all categories on the Wisconsin card sort test. There have been no medical complications of ketamine administration to date. Out of the 18 subjects administered ketamine 0.5 mg/kg over 40 minutes, 8 complained of blurred vision and two subjects vomited. Both the individuals who vomited were noted to have horizontal nystagmus. There have not been adverse psychological reactions in any of the healthy subjects. There is no doubt that ketamine has clear and, in some cases, dramatic effects upon cognitive function. Some people find these effects pleasant or interesting and others find these effects frightening. In prior studies, all subjects have been thoroughly prepared for possible ketamine response prior to testing and debriefed at the end of each test day. As a result, only two subjects terminated their participation in either study prematurely. No subject has had adverse or lingering responses to ketamine following a test day. Also, none of the subjects experienced "flashbacks" to their ketamine experiences following a test day. These findings are very consistent with the earlier work of Domino and his colleagues. Thus, ketamine appears to be safe and, despite the intensity of its short-term behavioral effects, well tolerated. The extent to which the effects of ketamine are perceived as unpleasant is context dependent and can be reduced by preparing individuals in advance for the possible responses to ketamine. The response to ketamine appears to be reduced by a number of medications, including benzodiazepines and antipsychotic agents.

Since 1989, Yale researchers have administered ketamine to over 140 healthy subjects, 30 recovering alcohol patients and 20 patients with major depression. Adverse effects in response to ketamine infusion have been **mild and transient**, with no evidence of any clinically significant adverse side effects. We have reported 8 adverse events associated with ketamine administration to the Institutional Review Boards of Yale and/or the West Haven VA since October of 2000. None was considered serious and all resolved shortly after discontinuation of the ketamine infusion or within two weeks of the ketamine test day. Adverse events included nausea and vomiting, sedation, hypotension, insomnia and nightmares, headaches, visual and somatosensory perceptual alterations, strong paranoid feelings, and anxiety.

None of the patients or healthy subjects studied to date has had any *long-term* adverse consequences as a result of ketamine administration. This impression is supported by follow-up data up to 2 years on 132 healthy subjects participating in ketamine studies at Yale

University and at Washington University at St. Louis (unpublished data). We examined follow-up assessments collected in a sub-sample of 132 healthy subjects who returned for subsequent testing over a duration of 1 week to 2 years. These subjects completed a similar battery of assessments when they reappeared as they completed in their earlier testing. In this analysis, no significant changes occurred in any measure between their initial and follow-up assessment.

In a previous study where ketamine was administered to depressed subjects there were adverse effects, though none were severe and none persisted beyond 110 minutes. Conversely, there was a significant transient improvement of depressive symptoms.

Blood drawing/intravenous placement: Bruising or thrombosis can occur with placement of the intravenous line. A total of 30cc will be drawn at baseline to ensure subject health before entering the study. The risks of blood draws include brief pain at the time of needle insertion, bruising, swelling at needle site and rarely, fainting or infection. The amount drawn is considerably less than 500 cc, the amount approved by the Red Cross.

Psychiatric evaluation, rating scales and questionnaires: These are all non-invasive, should add no risk, and have been used without difficulty or adverse events in previous studies with a similar population. The major disadvantage is the time taken to complete them.

Clinical Deterioration: There is a risk that a participant may experience an increase in SAD or depressive symptoms due to the natural course of the illness or poor response to ketamine administration. Because subjects will be asked to refrain from changing any psychotropic medication over the course of the study, clinical progress will be monitored closely with frequent HAM-A and HDRS ratings and frequent contact with clinic personnel. The following are criteria for evaluation and possible pharmacological and/or non-pharmacological treatments: (1) An increase of 25% in HAM-A score at any time over the course of treatment (lasting beyond acute administration studies), (2) new-onset of suicidal ideation or an increase in passive suicidal ideation.

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

Protection of subjects: Effective screening should exclude individuals who will be placed at greater risk in this study because of medical conditions or psychiatric symptomatology. A detailed medical and psychiatric history, physical examination, and laboratory studies must be conducted prior to commencing the study. All the tests will be done in the presence of constant medical supervision with experienced nursing and technical staff.

Ketamine Administration: The most common side effects of ketamine are (1) Elevated blood pressure, breathing rate and pulse rate, (2) Local pain at injection site and temporary rash and (3) A variety of temporary psychological symptoms including, but not limited to anxiety, sadness, disorientation, insomnia, flashbacks, hallucinations, and psychotic-like symptoms. These types of reactions have occurred in approximately 12% of patients given higher doses of ketamine when used for anesthesia. These symptoms usually last no more than a few hours. The most serious possible side effects of

ketamine use are (1) Substance abuse/dependence, (2) Elevations in intraocular pressure that could lead to vision problems, (3) Allergic reaction and (4) Elevation in blood pressure that could result in stroke, heart problems and death. All the serious possible side effects of ketamine are rare. As a precaution all patients will be administered ketamine and monitored at the Clinical Neuroscience Research Unit for 3 hours following ketamine infusions. If the side-effects do not dissipate we will additionally offer patients hospitalization at Connecticut Mental Health Center for psychiatric side-effects or YNHH for medical side-effects.

In order to minimize these risks for research subjects, vital signs will be monitored regularly throughout and for the first hour following the ketamine infusion. Subjects will be monitored for at least 3 hours following ketamine infusion by Dr. Bloch. In the event, that a research subject has a significant psychiatric event requiring hospitalization, they will be treated on the Clinical Neuroscience Research Unit (the inpatient unit where the infusion takes place). Emergent medical care would be provided at Yale-New Haven Hospital which is directly across the street from the site of infusion.

The dose of ketamine established in prior research (0.5 mg/kg over 40 minutes) will be used in this study to minimize risks. Yale New Haven Hospital policy currently does not require any special credentialing privileges to administer ketamine at sub anesthetic doses such as those utilized in this study. A study doctor and nurse will be at the bedside at all times during the infusion and recovery. During the infusion, heart rate, respiratory rate, oxygen saturation, level of consciousness, and pain are monitored continuously and blood pressure is monitored every 5 minutes. Heart rate, respiratory rate, blood pressure, oxygen saturation, and pain are documented every 15 minutes. During the recovery period, the patient is monitored every 15 minutes for at least one hour after the last dose of the sedative agent is given. The patient will remain on this sedation for 3 hours following the ketamine infusion.

Patients who receive ketamine will not be permitted to drive home after the infusion. Research staff will arrange transportation for the patient. Patients will be allowed to stay on the Yale Clinical Neuroscience Research Unit (CNRU) the night of the ketamine infusion. All participants will be asked not to engage in demanding work for the first 3 days after the ketamine infusion. If participants develop psychiatric symptoms, we may admit them to the hospital. Hospitalization may be involuntary if patients are in danger of harming themselves or others.

The consent forms will provide a description of what participants may experience during the intravenous ketamine infusion at a dose of 0.5 mg/kg over the course of 40 minutes, so that they will be well prepared for possible responses to ketamine. Participants will be told that some people have reported mildly decreased concentration or a “hangover” on the day after ketamine, but since subjects will not be allowed to drive home, there is less of a concern regarding driving. A research nurse will be present throughout the study to monitor the patient’s response and note any changes in physical or mental state. A research clinician will be present throughout the study to offer support and to help clarify the progress of the test day in case the medication causes feelings of confusion. A research doctor will also be available. The physician would be informed in case of any alarming changes in the patient’s physical or mental state. The research nurse will also offer support and provide consistent “reality testing” for individuals experiencing confusion or transient psychosis.

Intravenous and oral diazepam will be kept available to control markedly distressing behavioral effects of ketamine, should they emerge.

All participants will be asked to contact us at any time if any unpleasant effects occur. All participants will be given wallet-sized cards, which provide contact information. The cards will identify the Yale Human Investigation Committee number for the study, the study PI (Michael Bloch, MD with phone number), off-hour contact number (203-974-7560, CNRU inpatient nursing station), Connecticut Mental

Health Center Investigational Drug Service phone number, and regular hours telephone numbers of their study physician and research support staff (Jerome Taylor, MD 203-936-7716), should unpleasant effects occur after the subject has left the testing facility. All participants are contacted 1, 2, 3, 5, 7, 10, 14, 21, and 28 days after each infusion for safety reasons. In addition, participants will be contacted 1, 2, 3, 5, 7, 10, and 14 days after each infusion to administer symptom ratings. Participants will be instructed and encouraged to contact the treatment team between scheduled meetings should their distress worsen.

In order to enroll in the study, patients must not have a lifetime history of substance abuse or dependence, thereby reducing the risk of ketamine substance abuse/dependence by study participants.

Blood drawing/intravenous placement: The risks of blood draws and intravenous line placements are rare, and when these are done under sterile conditions by trained personnel the occurrence is even more remote.

Psychiatric evaluation, rating scales, questionnaires, speech tasks, and attention bias tasks: In order to minimize risks associated with the psychiatric ratings and ensure the accuracy of reporting, these measures will be administered by a trained research nurse and supervised by a study physician. During the impromptu speech, participants have the option to stop the speech at any time if they experience significant distress.

Clinical deterioration: If a participant shows significant worsening of symptoms, he or she will be evaluated for clinically appropriate pharmacological and non-pharmacological treatments by a clinic psychiatrist and followed until successful contact with a community provider is made. Patients will be informed that the decision to initiate a course of psychotropic medication will not affect their eligibility to participate in future studies, to receive treatment at the Connecticut Mental Health Center or Yale, or to receive treatment on a private basis from a referring clinician.

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? This is a moderate risk study.
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? N/A
    c. Copy, paste, and then tailor an appropriate Data and Safety Monitoring Plan from http://www.yale.edu/hrpp/forms-templates/biomedical.html for
        i. Minimal risk
        ii. Greater than minimal/moderate risk
        iii. High risk

Moderate Risk DSMP

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

The principal investigator will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency which must be conducted at a minimum of every 6 months (including when re-approval of the protocol is sought). During the review process, the principal investigator (monitor) will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator or the IRB have the authority to stop or suspend the study or require modifications.

2. The risks associated with the current study are deemed moderate for the following reasons: (choose those that apply)

1. We do not view the risks associated with the ketamine infusion as minimal.
2. Given the now established safety and validity of the current dose of ketamine in our prior work, we do not view the proposed studies as high risk.

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

3. Attribution of Adverse Events:
Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator (Michael H. Bloch, MD) 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).

4. Plan for Grading Adverse Events:

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

1. Mild adverse event
2. Moderate adverse event
3. Severe

5. Plan for Determining Seriousness of Adverse Events:

Serious Adverse Events:
In addition to grading the adverse event, 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:

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

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

6. Plan for reporting Reportable Adverse Events and other unanticipated problems involving risks to subjects or others to the IRB

The principal investigator will report the following types of events to the IRB: a) adverse events that are serious or life-threatening AND unanticipated (or anticipated but occurring with a greater frequency than expected) AND possibly, probably or definitely related to the drug/device/intervention; and b) 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 IRB in accordance with IRB Policy 710, using the appropriate forms found on the website.

7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), and funding and regulatory agencies, and regulatory and decision-making bodies.

For the current study, the following individuals, funding, and/or regulatory agencies will be notified (choose those that apply):

X All Co-Investigators listed on the protocol.

X Food and Drug Administration

The principal investigator (Michael H. Bloch, MD) 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.

We will use a paired t-test to compare average improvement over the first 3 days following infusion between ketamine and saline. Ketamine greatly reduces anxiety and depressive symptoms in MDD with an effect size of 1.4-1.5 in similarly designed saline controlled studies (Zarate, Singh et al. 2006). If ketamine proves to be as efficacious in SAD as it is in MDD, a sample size of 18 would allow a placebo to ketamine comparison study to have statistical power greater than 0.80 to detect a statistically significant change at the $\alpha = 0.05$ level (Cohen 1988). However, it is quite possible that the benefits of ketamine will be smaller in SAD than depression. Therefore, even if the results of our primary analysis are not statistically significant, we would consider having 6 of 18 patients exhibiting a response to ketamine (but not placebo) during the first week following infusion as sufficient evidence towards conducting a more definitive trial. Treatment response is defined as at least a 30% reduction in VAS scores anytime in the first 3 days following infusion.

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 (Ketalar) has USDA approval as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. The drug is also indicated for the induction of anesthesia prior to the administration of other general anesthetic agents or to supplement low potency agents, such as nitrous oxide. In this study, ketamine will be used for a therapeutic purpose. Nonetheless, Dr. Pittenger holds the research license for administering this controlled substance in a non-therapeutic research study.

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: **N/A.**

a. What is the Investigational New Drug (IND) **number** assigned by the FDA?

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

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

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 is a medication approved by the Food and Drug Administration to be used as an anesthetic. It is a dissociative anesthetic that has been used in humans since the late 1960's (32). Despite extensive experience there is no clear evidence of long-term toxicity associated with ketamine administration (33). Please see Risks and Minimizing Risks Sections labeled “Ketamine Administration” above.

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

Ketamine (Ketalar) will be obtained from the CMHC Research Pharmacy

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

If yes, by whom?

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.

Ketalar is chemically designated *d,l* – 2- (0-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride. It is formulated as a slightly acidic (pH 3.5-5.5) sterile solution for intravenous or intramuscular injection in concentrations containing he equivalent of either 10, 50, or 100 mg ketamine base per milliliter and contains not more than 0.1 mg/mL Phemerol® (benzethonium chloride) added as a preservative. The 10mg/mL solution has been made isotonic with sodium chloride. The medication will be obtained and stored at the CMHC research pharmacy, and will be picked up by investigators on the morning of infusion.

Check applicable Investigational Drug Service utilized:

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

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.

Since this is a crossover trial, all subjects will receive both ketamine and placebo during the course of the study. A placebo control is necessary because there is a significant improvement with time and to treatment expectancy that occurs in anxiety disorders. Using a crossover design allows all subjects to get the research medication being studied in the protocol, yet provide an appropriate comparison condition.

Before beginning the study, participants will be informed of typical first-line treatments for SAD. Generally, one would try all three first line treatments sequentially followed by an MAOI as standard of care treatment(Pilling, Mayo-Wilson et al. 2013). However, roughly one-third to one-half of patients with generalized SAD do not experience significant clinical benefit from the combination of first-line interventions such as pharmacotherapy with selective serotonin reuptake inhibitors (SSRI), venlafaxine, or cognitive behavioral therapy (CBT) (Blomhoff, Spetalen et al. 2001, Davidson 2004, Baldwin, Anderson et al. 2005). Benzodiazepines, gabapentin, pregabalin, and monoamine oxidase inhibitors phenelzine and moclobemide are also effective in the treatment of social anxiety; however, to our knowledge, there are no randomized, placebo-controlled studies that examine the treatment of SAD patients who do not respond to first-line treatments. Moreover, aside from benzodiazepines, which have significant abuse potential, the medications often take at least a week for the patient to experience

benefits. This delay in anxiolytic effect coupled with side effects, which often begin immediately, can lead to premature discontinuation of these treatments. Finally, there is little evidence that combination of interventions (pharmacologic or psychotherapeutic) is effective(Blanco, Bragdon et al. 2013) (Blomhoff, Spetalen et al. 2001, Baldwin, Anderson et al. 2005).

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

One dose of IV saline will be given, and the patient will not receive the ketamine infusion one month (psychotropic medication changes are not allowed for the duration of the study – two months).

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

Anxiety symptoms may not improve or even worsen depending on the clinical course of illness. Subjects have the option of withdrawing from the research protocol at any point if their symptoms worsen. Additionally, inpatient hospitalization resources are available to the investigator if subject's symptoms worsen to the point of requiring inpatient hospitalization as part of the protocol.

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

As stated in the "Minimize Risk" section under "Clinical Deterioration above, if a participant shows significant worsening of symptoms, he or she will be evaluated for clinically appropriate pharmacological and non-pharmacological treatments by a clinic psychiatrist and followed until successful contact with a community provider is made. Patients will be informed that the decision to initiate a course of psychotropic medication will not affect their eligibility to participate in future studies, to receive treatment at the Connecticut Mental Health Center or Yale, or to receive treatment on a private basis from a referring clinician.

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.*

Dr.Pittenger holds a Laboratory Research License for use of a controlled substance in an on-therapeutic study involving human subjects.

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 is a controlled substance with the potential for abuse and/or psychiatric symptoms if used chronically. Furthermore, ketamine is administered IV in this study, which is untenable on an outpatient basis.

B. DEVICES - NA

SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

a. targeted for enrollment at Yale for this protocol 18

b. If this is a multi-site study, give the total number of subjects targeted across all sites
NA

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

☒ Flyers	☐ Internet/Web Postings	☐ Radio
☐ Posters	☐ Mass E-mail Solicitation	☐ Telephone
☒ Letter	☒ Departmental/Center Website	☐ Television
☒ Medical Record Review	☒ Departmental/Center Research Boards	☐ Newspaper
☐ Departmental/Center Newsletters	☐ Web-Based Clinical Trial Registries	
☒ YCCI Recruitment database	☒ Clinicaltrials.gov Registry (do not send materials to HIC)	
☐ Other (describe):		

3. Recruitment Procedures:

a. Describe how potential subjects will be identified. – Patients with Social Anxiety Disorder in the Yale Center for Anxiety and Mood Disorders Clinic will be recruited for this study. Additionally, some subjects will respond to the contact phone number on the clinicaltrials.gov trial listing, flyers, or postings on the departmental website/YCCI recruitment database. We will also reach out to local providers and leaders of local social anxiety groups by letter to inform them of our study.

b. Describe how potential subjects are contacted. Clinicians at the clinic will be informed about the opportunity and asked to inform their patients about the opportunity if appropriate. Potential subjects interested in the trial will initiate first contact with the study recruitment coordinator or another member of the research team.

c. Who is recruiting potential subjects? Co-investigators David Klemanski, PhD and Jerome Taylor, MD will inform clinicians at the clinic about the opportunity and may ask patients directly if they are seeing the patients clinically.

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:

A brief psychiatric and medical history will be collected during telephone screening including Axis I diagnoses, medical and neurologic diagnoses, as well as recent medication and psychotherapy changes. All information will be stored in locked cabinets/password protected computer in an office that is locked. Information that will breach subject confidentiality will not be shared. Rather, data will only be released upon written consent of the subject and will be available for review by the Yale human Investigation Committee. We will hold paper files for seven years at which point they will be destroyed.

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 (except year) 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.
Jerome Taylor, MD is to start seeing a few patients at the clinic.

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: __X____

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

I. We are requesting a waiver of HIPAA authorization for recruitment purposes only. Subjects will be initially recruited through clinicians at Yale Anxiety and Mood Disorders clinic in the Yale University Psychology Department and the clinicaltrials.gov registry. We will need to use PHI such as name, telephone number and email addresses to schedule initial screening interviews. It would be impractical to coordinate initial subject enrollment and recruitment without this data.

II. Signed authorization is impractical because initial screening of patients recruited through clinicaltrials.gov or clinician referral may occur over the telephone or email.

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.

Michael Bloch, MD; Jerome Taylor, MD, and Angeli Landeros-Weisenberger, MD.

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.

   Investigators will obtain consent during a screening visit at the Yale Child Study Center. During this visit, all aspects of the study will be discussed and the inclusion criteria will be explained.

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.

    Patients with SAD are considered capable of consent. Individuals with limited capacity to consent will not be enrolled in the study. The principal investigators and co-investigators responsible for consenting potential subjects will use their clinical judgment to determine whether potential subjects have the capacity to consent. Patients must be able to understand the study protocol, appreciate and rationally manipulate the risks and benefits, and verbalize their consent.

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.

    The Compound Authorization and Consent form is included in this application

12. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. Translated copies of all consent materials must be submitted for approval prior to use.

    Non-English speaking subjects will not be enrolled in this pilot study because the number of subjects is small and translating the rating scales and employing trained personnel to administer the assessments would be too time-intensive for this sample size.

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 for those subject who may call in with an interest from flyers or clinicaltrials.gov**

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 <u>Entire Study</u> (**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. **<u>Full waiver</u>** <u>of consent:</u> (No consent from subjects will be obtained for the activity.)

☐ **Requesting a waiver of consent for <u>Recruitment/Screening</u> 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?
PHI about subjects will include name, age, diagnosis, medical record data, results of physical examination including EKG information, laboratory tests, psychiatric rating scores, and performance on psychiatric tests (impromptu speech and attention bias tests). The urine toxicology results will be placed in the research study record. The subject will have a medical record at CMHC. Since the baseline urine toxicology and lab results will be collected during a visit at CMHC, the results of this test will become part of the CMHC medical record. This will be disclosed to the subject in the consent form and the investigator has obtained a Certificate of Confidentiality to protect all sensitive information connected with this study.

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

All study ratings completed during study visits, histories obtained at screening and medical records pertaining to study procedures are secured in locked files and stored on password-protected computers. Since this is an investigator-initiated study, the PI and study team will develop Clinical Research Forms (CRFs) for this study. These forms will be labeled with a unique random study code that cannot identify the patient. The key linking the code to the subject's identifiable information will be kept in an electronic excel file which is kept in a password protected file, on a password protected computer on the secure Yale server. A paper copy of this "master file" will be kept in a locked file cabinet as noted above. This master file will be kept separately from any coded data so that the identity of the participant will not be disclosed. Information which is required to be part of the medical record will be filed into the CMHC medical record. If a medical record has not been created, one will be created with this visit. The results of the medical and psychiatric evaluations conducted as part of this research will be available to clinicians caring for the subject unless the participant requests otherwise. The Yale Human Investigation Committee may review records of this research. In the case of published reports of this study, the identities of all participants will be protected.

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?

All of the information obtained from subjects in this research study will be locked clinic files or on a password protected server to insure confidentiality. Also, the methods utilized include storing identified data separately from that which need not be identified, storing medical records according to CMHC policy, and utilizing a secure server.

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

*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.

Data will be kept in a locked filing cabinet whose access is only obtainable by study personnel and electronic clinical data will be kept on a password protected server. The PI will also conduct periodic assessments to ensure that confidentiality provisions established at the onset of the study are maintained throughout the study and during data analysis. Additionally, all staff involved in the handling of subject data are/or will be trained on the requirements of HIPAA Privacy Rule and Human Subject Protection. If the PI should leave Yale, the PI will collaborate with his Department Chair and Faculty Advisor to ensure that proper and continued protection of individually identifiable information and protected health information continues.

After a period of five years these files will be destroyed by ITS approved methods or de-identified to protect subject confidentiality. All identifiable data will be destroyed by Dr. Jerome Taylor when the research is completed. Paper will be shredded via the confidential CMHC bins and all electronic files will be deleted or edited so that there is no identifiable information.

Impromptu speeches will be videotaped during the study. The videotapes will be kept for 5 years. After that time they will be destroyed or de-identified.

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)

In addition to study investigators, members of the HIC, the study sponsor, and the FDA may have access to study data.

g. If appropriate, has a Certificate of Confidentiality been obtained?
A Certificate of Confidentiality has been obtained to protect the drug toxicology results. Where possible, information will be destroyed that may link the subject to illicit drug use. Since a CMHC chart will need to be created for these subjects by virtue of their visit to the site, there is a concern that these results could be traced back to the subject. Subjects who test positive on the toxicology test will not be able to participate in this protocol. Subjects will be encouraged to seek treatment for their substance use, as appropriate.

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.

Although considered unlikely to be encountered, limits to confidentiality such as mandatory reporting requirements for abuse of children or the elderly will be complied with.

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.)

There may be no direct benefit from a subject's participation in this study. The potential benefits to society of these investigations are considerable. SAD continues to be a major public health problem with tragic cost to the individual, the family, and the community. The present study may improve our understanding of SAD by providing a pharmacologic rationale for developing novel treatments.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

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

The subject may discuss other non-research treatments for SAD with their practitioner or remain on their current standard of care regiment. This will include a discussion of pharmacologic, psychosocial, and somatic treatments.

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.

Participant payments will be $750 per subject if the study is completed. Participants will be compensated $25 for each of 14 baseline and follow-up assessments and$100 for participating in each of 2 infusion days. They will also receive an additional $200 for completion of all study procedures. Additionally, transportation to and from the appointment on infusion days will be provided to subjects. Subjects who are traveling from a distance will be offered lodging and transportation reimbursement up to $500.

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.

The study drugs and all medical treatment in this research study will be provided free of charge. There are no charges for the study visits, including the cost of transportation on infusions days and transportation and lodging up to $500 for subjects traveling from a distance. Costs to the participant are thus limited to the cost of transportation to and from study appointments other than infusion days.

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?

If a physical injury or illness occurs as a direct result of participation in this study, study physicians and nursing personnel will be provided emergency medical care and ensure that research participants receive prompt evaluation and medical treatment as necessary. In severe cases this may involve a transfer to Yale-New Haven Hospital emergency room. The cost of treatment for any such injury or illness will not be paid for through the study and will be the responsibility of the research participant.

   b. Where and from whom may treatment be obtained?

In the event of a significant medical emergency the participant will be transported to Yale New Haven Hospital. Should there be adverse psychiatric effects as a result of the study they will receive either inpatient treatment on the CNRU at CMHC or as an outpatient from the Yale Anxiety and Mood Disorders Clinic.

   c. Are there any limits to the treatment being provided?

In the unlikely event that any psychiatric care more intensive than regular clinic visits and a couple of nights of observation on the CNRU is required as a direct result of participation in this study, study personnel will provide emergent care and stabilization. Longer observation on the CNRU and more frequent clinic visits, if necessary in the short term may also be provided. If longer-term psychiatric care is required, beyond what is normally provided by a research clinic, then study personnel will provide referrals and otherwise endeavor to assist participants in arranging such care.

   d. Who will pay for this treatment?

The study investigators will provide additional short-term inpatient hospitalization that is needed to provide emergent care and stabilization following any adverse psychiatric events. Longer-term psychiatric care to alleviate a participant's symptoms below their severity when entering the study or medical treatments provided at other facilities will be billed to the

participant or the participant's insurance company. Participants do not give up any of their legal rights by signing the consent forms.

e. How will the medical treatment be accessed by subjects?

As part of the study protocol, participants will be systematically asked about any adverse events they experience and their SAD symptom severity by study personnel. They will also be instructed to inform study personnel if they believe they have suffered an adverse event or worsening of their SAD symptoms as a result of the protocol. Help in coordination of their outpatient psychiatric care for SAD is a regular part of the clinical care provided at the Anxiety and Mood Disorders Clinic. Participants are free to request this at any time.

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