

HIC# 1506016041



**YALE UNIVERSITY  
HUMAN INVESTIGATION COMMITTEE**

**Application to Involve Pediatric Human Subjects in Biomedical Research  
100 FR17 (2013-1)**

<p>Please refer to the HIC website for application instructions and information required to complete this application. The Instructions are available at <a href="http://www.yale.edu/hrpp/forms-templates/biomedical.html">http://www.yale.edu/hrpp/forms-templates/biomedical.html</a></p> <p>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.</p>	<b>HIC OFFICE USE ONLY</b>	
	DATE STAMPED-RECEIVED	PROTOCOL NUMBER

**SECTION I: ADMINISTRATIVE INFORMATION**

<b>Title of Research Project:</b> Efficacy of Rapid-Acting NMDA Antagonist for Treatment of Adolescent Treatment Refractory Major Depressive Disorder and Anxiety Disorders			
<b>Principal Investigator:</b> Michael H. Bloch, MD		<b>Yale Academic Appointment:</b> Assistant Professor in the Yale Child Study Center	
<b>Department:</b> Yale Child Study Center			
<b>Campus Address:</b> Yale Child Study Center, 230 South Frontage Rd., New Haven, CT 06510			
<b>Campus Phone:</b> 203-745-9921	<b>Fax:</b> 203-785-7611	<b>Pager:</b>	<b>E-mail:</b> Michael.bloch@yale.edu
<b>Protocol Correspondent Name &amp; Address (if different than PI):</b> Angeli Landeros-Weisenberger, MD, 230 South Frontage Rd., New Haven, CT 06520 SHM-I-371			
<b>Campus Phone:</b> 203-737-4809	<b>Fax:</b> 203-737-5104	<b>E-mail:</b> angeli.landeros@yale.edu	
<b>Business Manager:</b>			
<b>Campus Phone:</b>	<b>Fax :</b>	<b>E-mail:</b>	
<b>Faculty Advisor:</b> (required if PI is a student, resident, fellow or other trainee) <input type="checkbox"/> NA		<b>Yale Academic Appointment:</b>	
<b>Campus Address:</b>			
<b>Campus Phone:</b>	<b>Fax:</b>	<b>Pager:</b>	<b>E-mail:</b>

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**Investigator Interests:**

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

See Disclosures and Management of Personal Interests in Human Research

<http://www.yale.edu/hrpp/policies/index.html#COI>

Yes       No

Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?

Yes       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:**

- |   |   |
|---|---|
| <input checked="" type="checkbox"/> Magnetic Resonance Research Center (MR-TAC) | <input type="checkbox"/> Yale University PET Center                   |
| <input type="checkbox"/> Yale Cancer Center/Smilow                              | <input type="checkbox"/> YCCI/Church Street Research Unit (CSRU)      |
| <input type="checkbox"/> Yale Cancer Center/Clinical Trials Office              | <input checked="" type="checkbox"/> YCCI/Hospital Research Unit (2)   |
| <input type="checkbox"/> Yale-New Haven Hospital                                | <input type="checkbox"/> YCCI/Keck Laboratories                       |
|   | <input type="checkbox"/> Yale-New Haven Hospital/Saint Raphael Campus |

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- Cancer Data Repository/Tumor Registry  
 Specify Other Yale Location: Yale Child Study Center

**b. External Location[s]:**

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

**c. Additional Required Documents (check all that apply):**

- \*YCCI-Scientific and Safety Committee (YCCI-SSC)  N/A Approval Date:  
 \*Pediatric Protocol Review Committee (PPRC) Approval Date:  
 \*YCC Protocol Review Committee (YRC-PRC) Approval Date:  
 \*Dept. of Veterans Affairs, West Haven VA HSS Approval Date:  
 \*Radioactive Drug Research Committee (RDRC) Approval Date:  
 YNHH-Radiation Safety Committee (YNHH-RSC) Approval Date:  
 Magnetic Resonance Research Center PRC (MRRC-PRC) Approval Date:  
 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. 3 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): Efficacy trial

4. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more

than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

- Clinical Research: Patient-Oriented  Clinical Research: Outcomes and Health Services  
 Clinical Research: Epidemiologic and Behavioral  Interdisciplinary Research  
 Translational Research #1 ("Bench-to-Bedside")

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Translational Research #2 (“Bedside-to-Community”)       Community-Based Research

5. Is this study a clinical trial? Yes       No

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

If yes, where is it registered?

Clinical Trials.gov registry

Other (Specify)

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

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

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

6. Does the Clinical Trials Agreement (CTA) require compliance with ICH GCP (E6)?

Yes  No

7. Will this study have a billable service? A Billable Service is defined as 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.

Contact [Thomas.debski@yale.edu](mailto:Thomas.debski@yale.edu).

8. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes X No \_\_\_ *If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform?

Yes – members of the Yale Pediatric Sedation team are credentialed to give all study drugs outlined in this protocol.

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure?

No

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

No

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
Jennifer B Dwyer, MD, PhD	Efficacy of Rapid-Acting NMDA Antagonist for Treatment of Adolescent Depression	AACAP Pilot Award	<input type="checkbox"/> Federal <input type="checkbox"/> State <input checked="" type="checkbox"/> Non Profit <input type="checkbox"/> Industry <input type="checkbox"/> Other For Profit <input type="checkbox"/> Other	<input type="checkbox"/> Grant-M# <input type="checkbox"/> Contract# <input type="checkbox"/> Contract Pending <input type="checkbox"/> Investigator/Department Initiated <input type="checkbox"/> Sponsor Initiated <input type="checkbox"/> Other, Specify:
Jennifer B Dwyer, MD, PhD	Efficacy of Rapid-Acting NMDA Antagonist for Treatment of Adolescent Depression	Yale Child Study Center Internal Award	<input type="checkbox"/> Federal <input type="checkbox"/> State <input checked="" type="checkbox"/> Non Profit <input type="checkbox"/> Industry <input type="checkbox"/> Other For Profit <input type="checkbox"/> Other	<input type="checkbox"/> Grant-M# <input type="checkbox"/> Contract# <input type="checkbox"/> Contract Pending <input type="checkbox"/> Investigator/Department Initiated <input type="checkbox"/> Sponsor Initiated <input type="checkbox"/> Other, Specify:
Amalia Londono Tobon, M.D.	Ketamine for Prolonged School Refusal in Adolescents: A Pilot Study	Yale Child Study Center Internal Award	<input type="checkbox"/> Federal <input type="checkbox"/> State <input checked="" type="checkbox"/> Non Profit <input type="checkbox"/> Industry <input type="checkbox"/> Other For Profit <input type="checkbox"/> Other	<input type="checkbox"/> Grant-M# <input type="checkbox"/> Contract# <input type="checkbox"/> Contract Pending <input type="checkbox"/> Investigator/Department Initiated <input type="checkbox"/> Sponsor Initiated <input type="checkbox"/> Other, Specify:

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Jennifer B Dwyer, MD, PhD	Efficacy of Rapid-Acting NMDA Antagonist for Treatment of Adolescent Depression	Thrasher Research Foundation: Early Career Award	<input type="checkbox"/> Federal <input type="checkbox"/> State <input checked="" type="checkbox"/> Non Profit <input type="checkbox"/> Industry <input type="checkbox"/> Other For Profit <input type="checkbox"/> Other	<input type="checkbox"/> Grant-M# <input type="checkbox"/> Contract# <input type="checkbox"/> Contract Pending <input type="checkbox"/> Investigator/Department Initiated <input type="checkbox"/> Sponsor Initiated Other, Specify:
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IRB Review fees are charged for projects funded by Industry or Other For-Profit Sponsors. Provide the Name and Address of the Sponsor Representative to whom the invoice should be sent. **Note: the PI's home department will be billed if this information is not provided.**

**Send IRB Review Fee Invoice To:**

Name:  
 Company:  
 Address:

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

	Name	Affiliation: Yale/Other Institution (Identify)	NetID
<b>Principal Investigator</b>	Michael Bloch, MD	Yale Child Study Center	Mhb32
<b>Role: Co-investigator</b>	Gerard Sanacora, MD, PhD	Yale Dept of Psychiatry	Gs59
<b>Role: Co-investigator</b>	Jennifer Dwyer, MD, PhD	Yale Child Study Center	Jd775
<b>Role: Co-investigator</b>	Angeli Landeros-Weisenberger, MD	Yale Child Study Center	Al495
<b>Role: Co-investigator</b>	Hilary Blumberg, MD	Yale Dept of Psychiatry	Hb62
<b>Role: Co investigator</b>	Wendy Silverman, Ph.D.	Yale Child Study Center	Wks9
<b>Role: Co investigator</b>	Eli Lebowitz, Ph.D.	Yale Child Study Center	Er132
<b>Role: Co investigator</b>	Amalia Londono Tobon, MD	Yale Child Study Center	Al868
<b>Role: Study Personnel</b>	John Giuliano, MD	Yale Dept of Pediatrics	Jsg22
<b>Role: Study Personnel</b>	Edward Vincent Faustino, MD, MPH	Yale Dept of Pediatrics	Evf5
<b>Role: Study Personnel</b>	Susan Quatrano	Yale Dept of Psychiatry	Ss438
<b>Role: Study Personnel</b>	Linda Spencer	Yale Dept of Psychiatry	Las78
<b>Role: Study Personnel</b>	Jennifer Johnston	Yale Dept of Psychiatry	Jj434
<b>Role: Study Personnel</b>	Judah Weathers	Yale Dept of Psychiatry	Jdw49
<b>Role: Study Personnel</b>	Jessica Johnson, BS	Yale Child Study Center	Jaj62

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Role: Study Personnel	Baris Olten	Yale Child Study Center	BO222
Role: Study Personnel	Shilpa Telang	Yale Child Study Center	SB2528

**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.**

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

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

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

\_\_\_\_\_  
PI Name (PRINT) and Signature

\_\_\_\_\_  
Date



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

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

\_\_\_\_\_  
Advisor Name (PRINT) and Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Advisor Name (PRINT) and Signature

\_\_\_\_\_  
Date

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**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 had 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

## SECTION V: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.  
*The purpose of this study is to determine the tolerability and short-term efficacy of a single ketamine infusion for the treatment of adolescents with 1) medication-refractory major depressive disorder (MDD) and/or 2) medication-refractory anxiety disorders (social anxiety disorder, panic disorder, generalized anxiety disorder and/or separation anxiety disorder).* We will conduct a crossover trial in which as many as 36 adolescents (18 with MDD and 18 with anxiety disorders) will be given a single infusion of ketamine (study drug) or midazolam (active control). MDD symptoms and anxiety symptoms will be monitored over a two-week period. If applicable, comorbid school refusal symptoms will also be monitored over a two-week period for both cohorts. A 2-week washout period will be required between infusion doses. Our primary outcomes will be 1) improvement in MDD symptoms (measured by Montgomery-Asberg Depression Rating Scale, revised (MADRS) score) 1 day after infusion, for the cohort of subjects enrolled in the MDD arm of this trial and 2) improvement in the anxiety symptoms (measured by the Multimodal Anxiety Scale for Children (MASC) acute physical symptoms subscale) for the cohort of subjects enrolled in the anxiety disorders arm of the trial. As secondary outcomes, we are also proposing to *(1) more comprehensively assess suicidal ideation as an additional efficacy outcome in the trial, (2) measure ketamine's effects on symptom constructs associated with suicidal ideation or behavior, including anxiety, anhedonia and hopelessness (3-8), (3) examine ketamine's effects on school-refusal behavior (SRB) that is associated with anxiety and depression and (4) examine ketamine's effects on frontal neural systems associated with suicidal ideation and behavior as well as anxiety using functional magnetic resonance imaging (fMRI) and a behavioral task that has previously demonstrated findings associated with suicide attempts in adolescents with mood disorders (9).*
  
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.

**Major Depressive Disorder (MDD):**

MDD is a significant pediatric health problem with a point prevalence of up to 8% and a lifetime prevalence approaching 25% by the end of adolescence (10-13). Adolescent MDD is associated with significant comorbidity including poor social and scholastic functioning, early pregnancy, and increased risk of physical illness and substance abuse (14-16). It is also linked with significant mortality, with an increased risk for suicide (the 3<sup>rd</sup> leading cause of death in 15-24 year olds) (10, 17). Treatment can be difficult, with 40% of patients failing to achieve remission from SSRIs (18). Of that SSRI-resistant population, nearly half remain depressed despite switching medications and adding psychotherapy (19, 20). Of those that do improve, 1 in 4 relapse within a year (21).

**Anxiety Disorders:**

Pediatric anxiety disorders (e.g. generalized anxiety disorder, social anxiety disorder, separation anxiety disorder and panic disorder) are some of the most prevalent psychiatric conditions in children and adolescents(22, 23). It is estimated that 15–20% of youth suffer from these disorders(22, 23). When not treated successfully, anxiety disorders are associated with significant short- and long-term impairment and tremendous societal costs (24-26). Childhood anxiety disorders are often precursors to additional subsequent anxiety disorders, major depression, substance abuse and suicide attempts (27, 28). Cognitive-behavior therapy and

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selective serotonin reuptake inhibitors have emerged as the most effective treatments for pediatric anxiety disorders. The Childhood Anxiety Multimodal Study (CAMS) demonstrated that both CBT and SSRIs were highly effective for childhood anxiety disorders and their combination was superior to each individual therapy (29). However, it is estimated that roughly half of children with anxiety disorders fail to achieve remission with available first-line treatment (30). Severe anxiety in childhood is associated with increased risk of depression, school refusal, substance abuse, suicide and reduced quality of life (31). Although first-line treatments are quite effective in pediatric anxiety additional treatments to benefit those children and adolescents who fail to benefit from these first-line treatments are urgently needed as other evidence-based treatment options are lacking.

### **Ketamine**

Evidence implicates the glutamate system in the pathophysiology of depression and anxiety. Ketamine, an NMDA receptor antagonist, has been demonstrated in multiple controlled clinical studies to have rapidly acting antidepressant, anti-anxiety and anti-suicidal effects (32-37) (see preliminary data section). In adult studies, ketamine has a robust average effect size of  $>1.2$  and an number needed to treat (NNT) of only 2.3 in the medication-refractory depressed population (1). While ketamine improves a range of depressive symptoms in adults, it notably reduces anhedonia (38), a symptom associated with poor therapeutic response in adolescent MDD (39). Ketamine also specifically reduces suicidality in adults (40), a dimension of adolescent MDD that is resistant to, or perhaps even increased, by SSRIs (41, 42). Similarly, several controlled studies in adults have suggested ketamine may be effective in reducing OCD and PTSD symptoms as well as comorbid anxiety symptoms in subjects with primary MDD. While the glutamate system continues to mature in adolescence (43), preclinical data suggests that ketamine reverses depressive phenotypes in adolescent rats (44). Due to its success in treating adult MDD, ketamine has started to be used for treatment-refractory affective disorders in adolescence in the community (45), despite having no prospective evidence available to guide clinicians. Similarly, we know of no controlled trials examining the effects of ketamine on anxiety disorders in children or adolescents.

We propose to conduct a study to explore the efficacy and time course of action of intravenous ketamine in the treatment of adolescent treatment-refractory 1) MDD and/or 2) anxiety disorders (generalized anxiety disorder, social anxiety disorder, panic disorder and separation anxiety)

### *Secondary Outcomes*

As secondary outcomes we will examine the effects of ketamine on (1) suicidal ideation and related constructs associated with suicidal behavior; (2) frontal systems involved in emotional face processing using fMRI that have been associated with depression, suicidal behavior and anxiety and (3) school refusal behaviors.

### **Suicidal Ideation and Related Constructs**

We are proposing a more thorough assessment of ketamine's effect on suicidal ideation and related constructs in order to provide data on whether ketamine has similar anti-suicidal properties in adolescents as has been demonstrated in adults. Throughout the trial we will regularly monitor the subjects. We will also examine ketamine's effects on biological markers of depressive, anxiety and suicidal behavior on neurocognitive testing. Specifically, we will examine ketamine's effects (compared to midazolam) in the both cohorts 24-hours after infusion on at least three neuropsychological tasks (46) (47); (1) Depression Implicit Association Tasks, (2) Anxiety Implicit Association Task, (3) Suicide Implicit Association Tasks (48), (4) Self

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Injurious Implicit Association Tasks. Stronger implicit association between death/suicide and self on the Death/Suicide IAT has been associated with not only previous history of suicide attempts but also future attempts.

**Emotional Face Processing on fMRI**

To investigate the brain changes that underlie ketamine's effects, we also propose to examine the effects of ketamine on responses within a frontal system during performance of an implicit emotional face processing task. Previous fMRI research using emotional face processing tasks has shown that it is affected by ketamine treatment and sensitive to differences between depressed and non-depressed adolescents and depressed adolescents with and without past suicide attempt history (9, 49-52). Emotional face processing tasks have also been demonstrated to be affected by anxiety disorders (53-55).

**School Refusal Behavior (SRB):**

MDD and anxiety are commonly associated with comorbid school refusal behavior. Nearly 5 to 10% of school aged children and adolescents have excessive SRB (56, 57). Long-term consequences of SRB include increased risk of substance abuse, suicide attempt, risky sexual behavior, and school dropout (58-60). Furthermore, SRB has high societal cost in the billions with proximal costs associated with poor academic performance or attendance, future underemployment and increased risk of criminal prosecution (60). Once refusal of school begins, children tend to continue this behavior, and returning youth to school becomes extremely challenging for children, parents, schools, and clinicians.

Although the population of children and adolescents with prolonged SRB is heterogeneous, up to 50% of these youth have comorbid anxiety and depression (61-63). Children with SRB and comorbid anxiety and depressive symptoms tend to refuse school primarily to avoid school-related stimuli that provoke a sense of general negative affectivity and/or to escape from aversive social or evaluative situations at school (64, 65). The longer the avoidance of school-related stimuli persists, the more difficult SRB become to treat and the greater the psychiatric, social and academic consequences. The SRB intervention literature is limited. A recent review of psychosocial interventions, predominantly cognitive behavior therapy (CBT) for SRB, identified only 8 small randomized controlled and quasi-experimental trials involving 435 participants. Results from this meta-analysis demonstrated that psychosocial interventions significantly increased attendance but did not significantly decrease anxiety in SRB (66). Other studies have examined medications including tricyclic antidepressants (TCAs) (67-70), serotonin reuptake inhibitors (71) (72, 73), and benzodiazepines (72), for SRB school refusal behavior in children and have reported inconsistent effects. Other than imipramine no medication, has shown significant benefit for school refusal in any randomized, controlled trial (67-70). Even when beneficial, antidepressant medications (e.g. TCAs, SSRIs) even when beneficial, take several weeks to reach full effects in improving anxiety and depression.

**PRELIMINARY DATA:**

Ketamine is an FDA-approved anesthetic agent that is commonly used to induce surgical anesthesia due to its low incidence of significant respiratory depression and hypotension. Its anesthetic effects are thought to be directly related to non-competitive inhibition of NMDA receptors. The majority of NMDA receptors in the forebrain consist of heterotetramers of the subunits NR1, NR2A, and NR2B; these subunits combine to form a cation channel, permeable to both sodium and calcium, that is dually gated by voltage and glutamate. Ketamine binds non-selectively to all common NMDA receptor subtypes at a site within the open channel and thereby

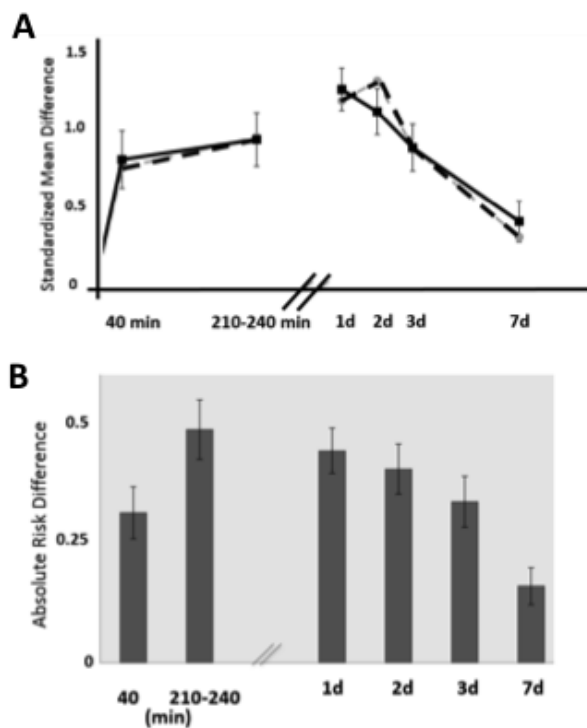
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blocks the entry of calcium.

Ketamine has a wide therapeutic window and has been used safely in Pediatrics for over 40 years for sedation prior to medical procedures and dentistry (74, 75). Ketamine is in fact used more frequently in Pediatrics than in adult populations, typically at doses of 1mg/kg – 4.5mg/kg iv over 60 seconds when used as an anesthetic agent. While there are no prospective studies of ketamine in pediatric psychiatric populations, the recently published retrospective report of ketamine use in pediatric bipolar depression did not describe any serious safety problems or adverse events associated with its use (45). Yale University has been safely using ketamine in research studies with adult psychiatric patients for over 20 years (32).

## Major Depressive Disorder

A placebo-controlled study completed here at Yale first demonstrated the surprising finding that a single dose of ketamine (0.5 mg/kg, intravenously) had rapid antidepressant effects in



**Figure 1:** A) Ketamine improves depressive symptoms in saline –controlled IV trials (dashed grey line), and in all pooled trials (solid black lines, including intranasal ketamine and midazolam controls) B). Ketamine induces an antidepressant response in a significant proportion of subjects. Adapted with permission (1)

depressed patients (33). In these subjects, ketamine infusion produced mild psychotomimetic symptoms and euphoria that dissipated within 120 minutes, while the antidepressant effects of ketamine infusion emerged over the first 180 minutes and persisted over 72 hours (33). Fifty percent of depressed patients receiving ketamine were treatment responders at Day 3 compared to 12.5% in the placebo infusion group (33). Another recent double-blind study performed at NIMH confirmed the rapid antidepressant effects of ketamine (34). In this second study, 72% of ketamine infused patients responded to treatment compared to no treatment responders in the placebo group (34). Since these initial studies at Yale, multiple controlled clinical studies have demonstrated that ketamine yields rapid antidepressant effect in unipolar and bipolar depression (33, 34, 76-78) (Figure 1) with an average effect size of 1.2 and a number needed to treat of only 2.3 (1). Ketamine’s antidepressant 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.

In order to provide proof of “target engagement” as pilot data for a larger, more definitive NIH-funded clinical trial examining ketamine’s suicide preventive properties, we also plan to examine ketamine’s effects on a frontal neural system associated with suicidal ideation and behavior. Specifically, abnormalities involving emotional processing neural circuitry are hypothesized to be particularly important in the development of adolescent suicidal behavior. Previous structural

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and functional neuroimaging studies have demonstrated abnormalities in a frontal neural system thought to contribute to suicidal ideation and behavior. These abnormalities include increased responses in anterior paralimbic cortex and amygdala to negative emotional stimuli that are hypothesized to underlie negative affect and anxiety, and decreased responses in more rostral and dorsal prefrontal cortex and striatal regions, including responses to positive stimuli that are hypothesized to increase anhedonia, and decreases in regions subserving impulse regulation (79). The interplay between neural circuits mediating emotional processing and impulsivity is central to our working model of adolescent suicidal behavior (79). We will specifically examine ketamine's effects on fMRI measures during an emotion face processing paradigm. Similar methods have previously elicited frontal neural system differences between adolescents and young adults who have made suicide attempts and who have suicidal ideation, from those without (9, 80, 81). Previous fMRI studies demonstrated elevated responses to faces depicting negative emotions in MDD subjects within paralimbic orbitofrontal, anterior cingulate and insular cortices and amygdala, and hypoactivation to happy faces within dorsal and rostral prefrontal cortex and striatal regions (50-52). In previous fMRI studies of depressed adolescents, the responses to negative emotional stimuli were shown to be higher in those with a previous history of suicide attempts than those without (9). A previous open-trial of 20 adults with treatment-refractory depression demonstrated normalization of blunted neural responses to happy faces 24-hours after ketamine infusion in subjects whose depressive symptoms responded to ketamine (49). With the current proposal, we plan to extend upon this previous work by examining with fMRI the changes in neural system responses with ketamine treatment and associated changes in suicide ideation and related constructs.

Due to its success in treating adult MDD and suicidal ideation, ketamine is now in use for treatment-refractory adolescents (45), despite having no data from controlled clinical trials to support this practice. Thus, carefully monitored prospective studies measuring ketamine's effects on suicidal ideation and constructs associated with suicide attempts, such as anxiety, anhedonia, hopelessness and depression, are urgently needed.

### **Anxiety Disorders**

Strong evidence also implicates the glutamate system in the pathophysiology of anxiety (82-86). The results of several clinical studies suggest that ketamine may also have significant anxiolytic effects in addition to antidepressant effects. As discussed earlier, ketamine has a robust average effect size of  $>1.2$  in reducing depressive symptoms and an NNT of only 2.3 in the medication refractory adults with major depressive disorder (90). Randomized controlled trials of ketamine for depressed adult patients demonstrated a significant reduction in comorbid anxiety symptoms, with a similar effect size of 1.4 (91, 92). Moderator studies in adults with depression have also demonstrated that adults with an anxious depression sub-type have an increased initial response to ketamine and longer time to relapse (93, 94). Adults with anxious depression relapsed significantly later than those with non-anxious depression (median  $\pm$  SE =  $19.0 \pm 17.9$  vs  $1.0 \pm 0.0$  days to relapse, respectively;  $\chi^2 = 9.30$ ;  $P = .002$ ) (93, 94). Ketamine has also been shown to reduce anxiety in adult patients with PTSD (95, 96) and OCD (97, 98). We also have recently completed a randomized, saline-controlled crossover study of ketamine in 18 adults with social anxiety disorder. Ketamine demonstrated a significant reduction in the CGI-I score at 1 day following infusion compared to saline (paired t-test  $t=2.78$ ,  $p=0.015$ ). Eleven of 18 subjects receiving ketamine were rated as minimally improved or better on the CGI 1-day following infusion compared to 2 of 17 receiving saline.

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

### **Overview:**

This is a double-blind, active control crossover study of 36 adolescents (13-17 years old) with treatment-refractory 1) MDD and/or 2) anxiety (social anxiety disorder, generalized anxiety disorder, panic disorder and/or separation anxiety disorder). Subjects will be assigned to the MDD treatment arm and/or the anxiety disorder treatment arm based on whether they meet inclusion criteria for each treatment arm (or both treatment arms). Subjects will receive similar symptom ratings regardless of which treatment arm(s) they are assigned.

Each subject will receive one infusion of ketamine (the study drug) and one infusion of midazolam (an active control agent). Due to the difficulty in blinding ketamine's acute effects and the high rate of placebo responses in depression and anxiety research, use of an active control is considered essential in establishing efficacy. There will be a 2-week period in between infusions in order to balance a potentially acceptable washout period with the risks of forbidding medication changes during the protocol. As shown in figure 1A, in adults, the antidepressant effects of ketamine typically subside by 7 days, and thus a 2-week period in between infusions is expected to be adequate. The study investigators, subjects, their parents, and research staff will be blinded to the infusion order. Infusion order will be determined by the Yale Investigational Drug Service, assigned in a balanced manner, and kept strictly confidential until the time of unblinding. Following each infusion, plasma ketamine metabolites and D-serine levels will be measured at 4 time points (last at 230 minutes post-infusion) and the participant's 1) MDD and/or 2) anxiety symptoms will be assessed for 2 weeks. Comorbid SRB (if applicable) will also be assessed for two weeks for participants in each of the cohorts. These psychiatric assessments will be conducted by a rater unaware of the clinical and side effect ratings on infusion day. Additionally, a separate rater will conduct side effect and psychotomimetic ratings for ketamine and midazolam throughout the study in order to reduce the risk of unblinding due to the psychometric and physiologic side effects associated with ketamine.

In addition, we will be performing Dr. Blumberg's paradigm for fMRI at baseline (before the first infusion) and 24 hours after each infusion to examine ketamine's effect on the frontal system during an emotional face processing task.

### **Screening/Baseline (Visit 1):**

After an initial phone screen to rule out any clear exclusion from the study protocol, potential subjects will be scheduled for a screening visit at the Yale Child Study Center. At the screening visit, a member of our research team will discuss all aspects of the study: its purpose, the procedures that will be performed, any/all risks of the procedures, possible benefits, and possible alternative treatments. If the patient is considered eligible for the study and agrees to enroll, the patient and his/her parent/guardian will be asked to sign the assent and parental permission forms, respectively. Once consented, the participant will undergo a standard clinical evaluation consisting of psychiatric history, physical, laboratory and mental status exams with one of the study doctors. This assessment includes collection of detailed information about all prior psychiatric therapies, including dose, duration of treatment, side effects, and partial efficacy. The participant and his/her parent/guardian will also receive a clinical diagnostic interview using the Mini International Neuropsychiatric Interview for Children and Adolescents



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(MINI-KID) (99). Additionally, the participant and his/her parent/guardian will complete clinical ratings related to the participant's 1) MDD symptoms and/or anxiety symptoms 2) symptoms of other commonly comorbid psychiatric conditions including school refusal behaviors. A medical assessment including vital signs, physical exam, baseline serum labs, urine drug screen, and urine pregnancy test will be completed prior to enrollment. The clinical assessment will take approximately 2 hours and the imaging will take about 1 hour and a half.

*Assessments and Ratings* (Table 1 provides a detailed assessment schedule)

*a. Medical Assessments:* 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, and routine urinalysis) will be completed. A total of 30 cc of blood will be drawn via venipuncture at this visit. In addition, an EKG will be performed and read in order to rule out any cardiac abnormalities.

Female subjects of childbearing potential will require urine/serum pregnancy testing prior to enrollment in the protocol. Because full confidentiality regarding pregnancy cannot be entirely guaranteed, these testing requirements and the limited scope of confidentiality will be made known to all subjects during the consent procedure. In this manner, young women who would not be comfortable with pregnancy testing or sharing the results of such testing can "opt out" of the study at the time of the initial consent, without having to declare specific reasons. According to CT state statutes for mandatory reporting, pregnancy in females **less than age of 13 years**, will be reported to parent(s) and to the State of Connecticut Department of Children and Family Services (DCF). Confidentiality with regard to pregnancy test results will be maintained for females **≥ 13 years**. If the pregnancy test is positive, the subject will not be able to participate in the protocol.

Additionally, in order to participate in this protocol, the pediatric subject will need to be asked questions about his/her prior and/or current illicit drug use and undergo drug testing (urine). Because drug use will exclude the minor from participating, the parent may ask why the child was asked not to participate or to leave the study. Therefore, parents and/or minors who are uncomfortable with questions about drug use can "opt out" of the study at the time of initial consent, without having to declare specific reasons.

Drug use information (**in the adolescent ≥ 13 years of age**) will not be shared with parents unless the study team feels that the minor is exhibiting behaviors that would pose an immediate threat to the minor or to others. The PI or co-investigator will ask the minor if the study team can share the drug testing results with parents. If the minor declines, the study team will refer the minor for evaluation based upon the clinical judgment of the Principal Investigator. In all cases, the safety and well-being of the minor will be protected. We will explicitly inform parents and minors, in the permission and assent documents, and orally with regard to these guidelines.

*b. Psychiatric Assessments:* Ratings will be conducted by trained research staff. A detailed description of the most common assessments included but not limited to, is listed below. The timing of the clinical assessments is depicted in Table 1 (located at the end of this Research Plan).

<b>All Subjects:</b>
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- 1) *Children's Depression Rating Scale, Revised (CDRS-R)*: a standardized rating scale that assesses depression severity in children and adolescents (100)*Montgomery-Asberg Depression Rating Scale (MADRS)*: a standardized rating scale that assesses depression severity in children and adolescents (101)
  - 2) *Columbia-Pleasure Scale for Children (CPS) (102)*: a standardized rating scale to assess anhedonia (103)*Treatment-Emergent Activation and Suicidality Assessment Profile (TEASAP)*: a rating scale designed to detect increased behavioral activation and suicidality (104)
  - 3) *Clinical Global Impressions (CGI)*: a widely used instrument used to assess overall severity of illness and symptom improvement on 1-7 point scales (105)
  - 4) *Multidimensional Anxiety Scale for Children (MASC)*: a multidimensional assessment of anxiety in children and adolescents (3)
  - 5) *Pediatric Anxiety Rating Scale (PARS)*: s a clinician-rated measure of anxiety severity in children and adolescents (106)
  - 6) *Clinician-Administered Dissociative States Scale (CADSS)*: self and interviewer administered items that evaluate dissociative symptoms (107)
  - 7) *Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID)*: structured clinical interview evaluating psychiatric disorders (99)*Beck Suicidal Ideation Scale (SSI-5)*: instrument to assess suicidal ideation(108)
  - 8) *Beck Hopelessness Scale (BHS)*: instrument to assess hopelessness(109)
  - 9) *Childhood Trauma Questionnaire (CTQ)*: a self-report screening measure for maltreatment histories in children (110)
  - 10) *Social Networks Interview (ASSIS)*:a brief measure of social supports (111)
  - 11) *Friendship Questionnaire*
  - 12) *Visual Analog Scale (112) for Anxiety and Mood Symptoms*
  - 13) *Affective Reactivity Index Self-report (ARI-S) (113)*
  - 14) *Columbia-Suicide Severity Rating Scale (C-SSRS)*: assessment of suicidal ideation and behavior in clinical and research settings (114)*Anxiety Disorders Interview Schedule (ADIS-IV)*: parent and child semi structured interview to assessment anxiety disorders (100)
- School Refusal Measures**
- 15) *School Refusal Assessment Scale- Revised (SRAS-R)*: child and parental questionnaire to evaluate etiology of school refusal behavior (115)
  - 16) *Hours attending school questionnaire*: hours per day of child attending school and expected hours of school attendance

c. *MRI Data Acquisition*: Subjects will be scanned on three different time points: 1) at Baseline, 2) 24 hours after the first infusion and 3) 24 hours after the second infusion. All scanning will be performed on a 3-Tesla Siemens Trio MR scanner. High resolution, 3-dimensional Magnetization Prepared Rapid Acquisition Gradient Echo T1-weighted sagittal structural images will be acquired: TR=1500ms, TE=2.83ms, FOV=256x256mm, matrix=256x256, slice thickness= 1.0mm no gap, 160 slices. fMRI will be acquired in alignment with the anterior commissure-posterior commissure plane with a single-shot echo planar imaging sequence: TR=2000ms, TE=25ms, matrix=64x64, FOV=240x240mm<sup>2</sup>, 40 3-mm slices no gap. fMRI data will be acquired while subjects perform the attention bias to treat task and the event-related emotional face processing task explained below, and if time permits two 5-minute resting runs. DTI data will be acquired in alignment with the fMRI data. Diffusion sensitizing gradients will be applied along 32 non-collinear directions with b-value=1000sec/mm<sup>2</sup>, together with an acquisition without diffusion weighting: b-value=0; TR=7400msec; TE=115msec; matrix=128x128; FOV=256mmx256mm and 40 3mm slices without gap. Youth participants will be asked not to drink any alcohol or use any other non-prescribed medications that could change brain function within 24 hours of the MRI scanning session. He/she will also be asked not to drink caffeinated beverages (coffee, tea, cola drinks) or smoke cigarettes the morning of the MRI scanning session.

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**Event-Related Emotional Face Processing Task:** In brief, subjects will view Ekman faces depicting neutral, negative and positive emotional expressions. Subjects will make a female/male button press determination (reaction time/accuracy recorded) for stimuli on-screen for 2sec, separated by 4, 8 or 12sec of cross-hair fixation: images of 5 men/5 women, each individual exhibiting all 3 expressions, 30 faces/run, 4 runs. Stimulus order is varied to control for sequential dependencies and counterbalanced within and across runs for expression, sex, identity and interstimulus interval.

**Neuropsychological Testing:** Subjects will perform various neuropsychological tests (46). Subjects will perform four tests, (1) Suicide Implicit Association Tasks, (2) Depression Implicit Association Tasks, and (3) Self Injurious Implicit Association Tasks and (4) the Anxiety Implicit Association Task. These tests will be administered first at Baseline, 24 hours after each infusion, and Day 7 and 14 after each infusion. The IAT are brief computer-administered tests that use people's reaction times when classifying semantic stimuli to measure the automatic mental associations they hold about various topics, in this case, life and death/suicide (48) (47).

**Infusion (Visit 2 & 10 – Day 0 & Day 14):** Subjects who, in the opinion of the principal investigator, are eligible to continue with the protocol procedures (after the results of the screening/baseline measures and diagnostics are considered) will present to the Hospital Research Unit (2) at Yale New Haven Hospital (YNHH) for the first infusion. The participant will be instructed to follow American Society of Anesthesiologists NPO guidelines the night before the infusion. These guidelines allow milk or a light meal 6 hours prior to the procedure and clear liquids up to 2 hours prior to the procedure. One hour prior to the infusion, two IV's will be placed and the patient will complete a screening interview with the Conscious Sedation physician. The participant's vital signs will be taken and they will receive a physical exam, EKG, rapid urine drug screen, and urine pregnancy test (if applicable). They will additionally complete a series of clinical ratings (see Table 1). 5cc of blood will be collected off of the non-infusion IV to measure pre-infusion ketamine metabolites and D-serine levels. One hour later, the infusion will be administered over a 40-minute period, either ketamine at a dose of 0.5mg/kg, or midazolam at a dose of 0.045 mg/kg (doses of both medications not to exceed a maximum total dose corresponding to a weight of 100kg). Ketamine and midazolam administrations will be performed on the HRU in the presence of a physician from the Pediatric Sedation Service, with access to airway and rescue equipment. The participant's vital signs will be monitored every hour for three hours following the infusion. 5cc blood collections off of the non-infusion iv will take place at 40 minutes (end of the infusion), 80 minutes, 110 minutes, and 230 minutes, post-infusion for analysis of ketamine metabolites and D-serine concentrations. The psychotomimetic side effects of ketamine or midazolam, and the mental status of the participant will also be monitored every hour for three hours following the infusion. In addition to the physician from the Pediatric Sedation service, a research nurse and psychiatrist will be present at all times during the procedure and recovery. This visit will take approximately 7-8 hours because the participant will receive the infusion as well as assessments and blood collection before and after the infusion. The total amount of blood collected on the infusion day will be 35cc (ranging from 0.77cc/kg for a 45kg adolescent (average weight of a 13-year-old girl or boy) to 0.53cc/kg (average weight of a 17-year-old boy)), all collected from the non-infusion IV to minimize discomfort. Fourteen days will separate the first and second infusions.

Ketamine has been used safely in pediatrics for over 40 years for conscious sedation and dentistry (75), however it does have significant risks. The most common side effects when ketamine is infused at the current rate and dose in adult studies are (1) increased blood pressure,

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respiratory rate, pulse, (2) pain/rash at the injection site, (3) temporary psychiatric symptoms including, but not limited to, disorientation, anxiety, dysphoria, flashbacks, hallucinations, and psychotic-like symptoms (which occur less frequently in younger patients (75)). These reactions are typically self-limited and occur in ~12% of adults given higher doses of ketamine than proposed in this study (116). The most serious side effects are (1) increased intraocular pressure, (2) allergic reaction, (3) laryngospasm, (4) elevated blood pressure resulting in stroke, heart attack, or death, and (5) substance abuse, all of which are rare (74, 75). These risks will be mitigated by providing comprehensive monitoring in the HRU during and 3 hours following the infusion, supervised by the YPCS Service with access to airway equipment. Ketamine has been studied in over 10,000 psychiatric patients in more than 100 separate studies. Our institution has had experience using ketamine safely in research studies involving adult psychiatric patients for the last 20 years. The Yale Pediatric Sedation Service uses ketamine in children and adolescents on a daily basis. This dose of ketamine is considered subanesthetic in both adults and children (74), and thus we expect minimal cardiorespiratory and neurologic side effects. Case report level data suggests a favorable side effect profile for intranasal ketamine for adolescents with refractory disorders (45). However, if side effects do not dissipate we will additionally offer patients hospitalization at Yale Psychiatric Hospital, Adolescent Unit for psychiatric side effects or YNHH for medical side effects.

Midazolam, the active control in this study, similarly has a robust history of use in pediatric sedation and dentistry (117-123). Also similar to ketamine, the dose proposed in the current study (0.045mg/kg over 40 minutes) is lower and slower than doses used in most pediatric sedation procedures (0.05 – 0.1mg/kg over 2 minutes)(122, 124). The most common side effects related to midazolam infusions are hiccups, nausea, vomiting, coughing, headache, and drowsiness. In doses higher than those involved in the proposed study, serious cardiorespiratory adverse events have occurred after administration of midazolam, including respiratory depression, airway obstruction, oxygen desaturation, apnea, respiratory arrest and/or cardiac arrest. In younger children, these higher doses have been associated with a risk for paradoxical disinhibition. Midazolam, like ketamine, has a short half-life, and important adverse events related either drug are not observed after 30 minutes following drug administration (74). The Yale Pediatric Sedation team has vast experience with this medication given its common usage, and will be present during the infusion and until the patient has reached an appropriate state of recovery. While the risks of serious adverse cardiorespiratory events are low given the dose chosen for this study, airway equipment and qualified physician personnel will be readily available.

Midazolam is the most appropriate control for ketamine in the proposed study, as the psychotomimetic effects of ketamine make it extremely difficult to blind when compared to saline (1). Specifically, the typically mild dizziness, nausea and dissociative effects on ketamine functionally un-blind subjects and investigators. As such, more recent ketamine studies have used midazolam as a control. Using an appropriate active control in this efficacy trial is critical to establishing genuine clinical efficacy for ketamine (and not just treatment expectancy or subject performance bias) before designing a larger trial, exposing more adolescents to this novel therapeutic intervention.

**Outpatient Follow-up: In-person (Visits 3, 7, 9 & 11, 15, 17 – Days 1, 7, 14 & 15, 21, 28)**

Subjects will return to the Yale Child Study Center for follow-up in person visits to monitor their symptoms of depression and/or anxiety and physical health. During these visits, the participant

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will complete a series of clinical ratings (see Table 1) to be conducted by a trained research staff member. Additionally, on Day 1 and 15 (visit 3 and 11), the psychotomimetic side effects of ketamine will be assessed; this assessment will be conducted by a separate rater than the clinical ratings. Imaging will be done and neuropsychological batteries will be applied (see Table 1) which will add about 1 to 2 more hour to those assessment days. All of the outpatient study follow-up visits will take approximately 1-2 hours.

**Outpatient Follow-up: Telephone (Visits 4-6, 8 & 12-14, 16 – Days 2, 3, 5, 10 & 16, 17, 19, 24)**

Each subject will schedule follow-up telephone calls with a member of the research staff to monitor his/her MDD symptoms and anxiety symptoms along with his/her comorbid school refusal symptoms (if applicable). During these telephone calls, participants will complete a series of clinical ratings (see Table 1) conducted by a trained research staff member. These telephone calls will take approximately 1 hour.

**Discharge from the Study:** In the event that a subject is judged to remain significantly depressed, anxious, presents with worsening school refusal behavior and/or is at an increased risk for suicidality at the end of the study, we will help make appropriate referrals to outpatient providers, intensive outpatient programs or inpatient psychiatric hospitals as clinically indicated. Investigators may continue close monitoring of significantly at risk subjects until such referrals are provided and available to the study participant. Participants who have completed the trial must have a CDRS score of less than 50 to be discharged from the study.

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Table 1: Overall Study Assessment Schedule

	SCREENING	Day 0 - First Infusion (Ketamine or Midazolam) and Day 0+14 - Second Infusion (Ketamine or Midazolam)							Day 1 and Day 1+14 (Day 15)	Day 2 and Day 2+14 (Day 16)	Day 3 and Day 3+14 (Day 17)	Day 5 and Day 5+14 (Day 19)	Day 7 and Day 7+14 (Day 21)	Day 10 and Day 10+14 (Day 24)	Day 14 (see 2nd inf) Day 14+14 (Day 28)
		-60m	0-40m	60m	80m	110m	120m	180m	230m						
		<b>INTERVENTION</b>													
Infusion		x													
<b>MEDICAL ASSESSMENT</b>															
Physical Exam	x								x						
EKG	x														
Blood Tests:															
Medical Screening Labs	x														
Metabolites		x	x		x	x		x							
Urine Tests:															
Urine pregnancy test	x	x													
Urine drug screen	x	x													
<b>CLINICAL RATINGS</b>															
<i>MDD Cohort</i>															
C-SSRS	x	x							x	x	x	x	x	x	x
CDRS-R	x	x							x				x		x
SSI-5	x	x							x		x		x		x
<i>SRB Cohort</i>															
ADIS-IV	x	x							x		x		x		x
Attendance	x	x							x	x	x	x	x	x	x
SRAS-R	x	x							x	x	x	x	x	x	x
<i>All participants</i>															
MINI-KID/K-SADS	x														
ASSIS	x														
CTQ	x														
Friendship	x								x				x		x
BHS	x	x							x		x		x		x
RCADS	x	x							x	x	x	x	x	x	x
TEASAP	x	x							x		x		x	x	x
MASC	x	x							x				x		x
VAS Anxiety	x	x		x			x	x	x	x	x	x	x	x	x
VAS Mood	x	x		x			x	x	x	x	x	x	x	x	x
MADRS	x	x		x			x	x	x	x	x	x	x	x	x
CADSS		x		x			x	x					x		x
CGI		x						x					x		x
CPS		x						x	x	x	x		x	x	x
ARI-S		x							x		x		x		x
<b>IMAGING</b>															
Development Questionnaire	x														
MFTQ	x														
Edinburgh Handedness	x														
WASI Vocab	x														
WASI Matrix	x														
Family History	x														
MRI Safety Questionnaire	x								x						
MRI Data Sheet	x								x						
ER1 and ER2	x								x						
fMRI Practice Test	x								x						
YMRS	x								x						
WASH-U-KSADS	x								x						
PANAS-SF	x								x						
DERS	x								x						
ERS	x								x						
BISII	x								x						
<b>NEUROPSYCH TESTING</b>															
IAT	x	x							x				x		x

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**Table 1: Assessment and Procedure Schedule for Trial Examining Ketamine's Effects on Suicidal Ideation in Adolescent Depression and Anxiety Symptoms.** *Medical Assessment: Electrocardiogram (EKG). Ratings Scales: Suicide Severity Rating Scale (C-SSRS)(114); Children's Depression Rating Scale, Revised (CDRS-R)(100); Beck Suicidal Ideation Scale (SSI-5)(108); Anxiety Disorders Interview Schedule (ADIS-IV)(100) ; School Refusal Assessment Scale, Revised (SRAS-R)(125); Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID 15/K-SADS)(99); Social Networks Interview (ASSIS)(99, 111); Childhood Trauma Questionnaire (CTQ)(110); Beck Hopelessness Scale (BHS)(109, 126); Revised Child Anxiety and Depression Scale (RCADS) (127); Treatment-Emergent Activation and Suicidality Assessment Profile (TEASAP)(104); Multidimensional Anxiety Scale for Children (MASC)(128); Visual Analog Scale (112, 129); Montgomery-Asberg Depression Rating Scale (MADRS)(101); Clinician-Administered Dissociative States Scale (CADSS)(107); Clinical Global Impressions (CGI)(105); Columbia-Pleasure Scale for Children (CPS)(44); Affective Reactivity Index (ARI-S) (113); Implicit Association Tasks (IAT) (47, 48).* Assessments at 60 and 120 minutes on infusion days will be conducted by a non-blinded study physician. We will additionally include the recommended self-report measures of sexual orientation and gender for all screened study subjects at baseline assessment.

#### 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.

Recruitment: Adolescents ages 13-17 years with medication-refractory MDD and/or treatment-refractory anxiety disorders will be recruited for this study. As many as 36 adolescents (18 with MDD and 18 with anxiety disorders) will be recruited through the Yale Child Study Center. The YCSC serves a large population of children with both MDD and anxiety disorders and has forged relationships with local schools for referrals of children and adolescents with MDD and

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Anxiety to the clinics. We will additionally employ letters to child mental health clinicians, educational lectures on adolescent MDD and anxiety disorders at mental health centers, and outreach to adolescent MDD and anxiety disorders researchers in the Boston-New York City area. Averages weights of subjects are anticipated to be 45-54kg for females 13-17 years old and 45-65kg for males 13-17 years old.

**6. Subject Classification:** Check off all classifications of subjects that will be targeted 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.

- |  |   |  |
|--|---|--|
| <input checked="" type="checkbox"/> Children   | <input type="checkbox"/> Healthy                                      | <input type="checkbox"/> Fetal material, placenta, or dead fetus |
| <input type="checkbox"/> Non-English Speaking  | <input type="checkbox"/> Prisoners                                    | <input type="checkbox"/> Economically disadvantaged persons      |
| <input type="checkbox"/> Decisionally Impaired | <input type="checkbox"/> Employees                                    | <input type="checkbox"/> Pregnant women and/or fetuses           |
| <input type="checkbox"/> Yale Students         | <input checked="" type="checkbox"/> 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 HIC Application Instructions section VII #2 for further requirements)

For adolescents, we will obtain consent from their parent (legal guardian) before enrolling them in the study. We will also require childhood assent for participation. A simple quiz testing the understanding of the protocol and important elements of informed consent is in place at the end of the consent form.

For females of child bearing potential we will conduct a urine pregnancy test prior to enrollment in the study. If the pregnancy test is positive, we will refer people to appropriate treatment and will exclude them from participation in the trial until completion of their pregnancy. For sexually active females, we will provide contraceptive counseling and refer them for contraceptive treatment if indicated. The acceptable methods of contraception will include oral birth control pills (OTCs), IUD, transdermal preparations, parenteral preparations, barrier contraceptive methods (i.e. condoms and diaphragm) and abstinence. As noted above, because full confidentiality regarding pregnancy cannot be entirely guaranteed, these testing requirements and the limited scope of confidentiality will be made known to all subjects during the consent procedure. In this manner, young women who would not be comfortable with pregnancy testing or sharing the results of such testing can “opt out” of the study at the time of the initial consent, without having to declare specific reasons. Pregnancy testing will be repeated on the day of both infusions.

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

*Inclusion Criteria for MDD Cohort:*

- 1) Meet DSM-5 criteria for Major Depressive Disorder by structured interview (MINI-KID).
- 2) Children’s Depression Rating Scale, Revised CDRS-R score  $\geq 40$  at screening



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- 3) Failure to achieve remission with at least 1 adequate prior antidepressant trial (e.g. SSRI, SNRI, or TCA), meaning at least 8 weeks at therapeutic dosing, including at least 4 weeks of stable dosing.

*Inclusion Criteria for Anxiety Cohort:*

- 1) Meet DSM-5 criteria for any of the following anxiety disorders: Social Anxiety Disorders, Generalized Anxiety Disorder, Separation Anxiety Disorder and/or Panic Disorder by structured interview (MINI-KID)
- 2) ADIS Clinical Severity Rating  $\geq 4$  (moderately severe) for any of the 4 included anxiety disorders
- 3) Failure to achieve remission with at least 1 adequate prior anxiolytic medication trial (e.g. SSRI, SNRI, or TCA), meaning at least 8 weeks at therapeutic dosing, including at least 4 weeks of stable dosing.
- 4) Failure to achieve remission with previous CBT or subject declines current CBT therapy.

*Inclusion Criteria for ALL:*

- 1) Male or female ages 13-17 years
- 2) Stable psychiatric medications and doses for the month prior to enrollment. Subjects may continue to engage in any ongoing psychotherapy.
- 3) Medically and neurologically healthy on the basis of physical examination and medical history.
- 4) Parents able to provide written informed consent and adolescents must additionally provide assent.

*Exclusion Criteria:*

- 1) Current inpatient hospitalization or active suicidal ideation requiring referral for inpatient hospitalization for safety.
- 2) History of psychotic disorder or manic episode diagnosed by MINI-KID
- 3) History of substance dependence diagnosis by MINI-KID (excluding tobacco) or positive urine toxicology.
- 4) Intellectual disability (IQ $<70$ ) per medical history
- 5) Pregnancy (urine pregnancy tests on the day of scans for menstruating girls).
- 6) Inability to provide written informed consent according to the Yale Human Investigation Committee (HIC) guidelines in English.
- 7) Safety contraindication to MRI scanning (for MRI portions of study only):
  - a) History of significant medical illness, particularly illness associated with possible changes in cerebral tissue or cerebrovascular.
  - b) History of neurologic abnormality, including significant head trauma (defined by loss of consciousness of  $\geq 5$ -minutes duration), seizure disorder, cerebrovascular or neoplastic lesion, or neurodegenerative disorder.
  - c) Contraindication to MRI scanning, e.g. presence of a ferromagnetic object, including orthodontic braces, or claustrophobia. All participants will be screened for metal objects by the same methods used for routine clinical MRI scanning.

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

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

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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 of the standard of care for children with MDD and/or anxiety disorders. The standard of care for MDD is initial treatment with an SSRI, which may be augmented with the addition of psychotherapy. The standard of care for anxiety disorders including Generalized Anxiety Disorder, Social Anxiety Disorders, Separation Anxiety Disorder and Panic disorder is evidence-based psychotherapy (e.g. CBT) and pharmacologic interventions (e.g. SSRI, SNRI, TCA). The research team will discuss the inclusion and exclusion criteria for each arm of the study. To be included in the MDD arm of this study, adolescents must have 1) failed their first treatment with an antidepressant medication (e.g. SSRI, SNRI, TCA or other accepted FDA-approved medications for MDD and 2) have a diagnosis of MDD by DSM-5 criteria and (3) have a CDRS-R score  $> 40$ . To be included in the Anxiety Disorders arm of this study, adolescents must have 1) failed pharmacologic treatment with an antidepressant medication (e.g. SSRI, SNRI, TCA), (2) been offered or failed a trial of CBT for anxiety; (3) Meet DSM-5 Criteria for Generalized Anxiety Disorder, Social Anxiety Disorders, Separation Anxiety Disorder and/or Panic disorder 4) have at least moderately severe anxiety disorders symptoms as measured by ADIS CSR  $\geq 4$ . If they agree to enroll in the study, they will sign the consent forms and undergo a standard clinical evaluation consisting of psychiatric history, physical, laboratory and mental status exams with one of the study doctors. The participant will also receive a clinical diagnostic interview using the MINI-KID, in addition to the baseline rating described in Table 1. A medical assessment including vital signs, physical exam, and urine drug screen and pregnancy test will be completed prior to enrollment.

Participants will be enrolled if 1) they have a clinical diagnosis of MDD, meeting DSM-V criteria, defined as having at least 2 weeks of depressed mood or loss of interest/pleasure, in addition to 4 or more of the following symptoms: change in sleep, loss of interest in daily activities, inappropriate guilt, decreased energy, change in concentration, change in appetite, psychomotor symptoms, or recurrent thoughts of death and a CDRS-R score  $> 40$  and/or 2) if they have clinical diagnosis of the following anxiety disorders (Generalized Anxiety Disorder, Social Anxiety Disorder, Separation Anxiety Disorder or Panic disorder). As a secondary outcome subjects with severe SRB defined by  $>25\%$  of absenteeism from school one month prior to initiation of study will also be followed if they meet the inclusion criteria with symptoms of MDD or Anxiety disorders.

Participants will be excluded from the study if they present with active suicidal ideation, a history of serious medical or neurological illness, current psychoactive substance dependence, mental disorders due to identified medical conditions, or non-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

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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 in both children and adults. 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(32). 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 adult 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. In this study, the absolute dose of ketamine is not to exceed 50mg, corresponding to a weight of 100kg. There have not been adverse psychological reactions in any of the healthy adult subjects. In the Yale Pediatric Sedation Team's experience, there have not been serious after-effects reported in follow-up phone calls after sedation with ketamine for medical purposes, although one family reported that their child had "weird dreams" the night following the procedure. 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.

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*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.

Additional risks of ketamine must be considered in the pediatric population, particularly in light of earlier studies with antidepressants in which pediatric patients experienced side effects/risks that adults did not. While ketamine specifically reduces suicidality in adults (40, 130) antidepressant medications have been associated with increased suicidal ideation in pediatric but not adult populations (42). In order to minimize the risk of increased suicidality in this study, subjects will (1) be excluded for active suicidal ideation at baseline, (2) undergo regular psychiatric assessments of suicidality and (3) have direct access to a child psychiatrist throughout the study. Additionally, any subject with significant psychiatric side effects will be offered hospitalization at one of Yale's inpatient psychiatric units.

As ketamine can be abused outside of its medical purpose, the risk of any potential addictive properties must also be considered. Ketamine has been used in the pediatric population for years, and the rates of ketamine addiction in the United States remain very low (131). The ketamine infusion protocol in this trial is given slowly at a low dose (smaller than what is used in anesthesia) to minimize psychotomimetic effects (the high) associated with it. Adult studies have not reported problems with addiction following this ketamine protocol (102). The potential risk of abuse will be mitigated by excluding subjects with a history of substance use disorder. Additionally, subjects and their parents will be warned about abuse potential in all consent/assent documents.

**Midazolam administration:** Midazolam, the active control in this study, is a medication that is approved by the Food and Drug Administration as a sedative for both children and adults. It is a benzodiazepine with a short half-life that is used commonly in pediatric sedation and dentistry (117-123) and it is frequently administered rapidly at higher doses than proposed in the current study (we propose 0.045mg/kg over 40 minutes versus sedation dosing of 0.05 – 0.1mg/kg over 2 minutes (122, 124)). In this study, the total midazolam dose is not to exceed 4.5mg, corresponding to a weight of 100kg. The most common side effects related to midazolam

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infusions are hiccups, nausea, vomiting, coughing, headache, and drowsiness. In doses higher than those involved in the proposed study, serious cardiorespiratory adverse events have occurred after administration of midazolam, including respiratory depression, airway obstruction, oxygen desaturation, apnea, respiratory arrest and/or cardiac arrest. In younger children, these higher doses have been associated with a risk for paradoxical disinhibition or agitation. Midazolam, like ketamine, has a short half-life, and important adverse events related either drug are not observed after 30 minutes following drug administration (74). The Yale Pediatric Sedation team has vast experience with this medication given its common usage, and will be present during the infusion and until the patient has reached an appropriate state of recovery, as is done for all pediatric sedation procedures at YNHH. While the risks of serious adverse cardiorespiratory events are low given the dose chosen for this study, airway equipment and qualified physician personnel will be readily available. The reversal medication, flumazenil, will also be available, which can rapidly abort the effects of midazolam should any untoward effects occur.

All benzodiazepines have the potential for physical and psychological dependence after prolonged use. The single infusion and low dose proposed in this study would not be expected to result in any physiologic dependence. Benzodiazepines as a class are also at risk to be abused for recreational use outside of medical purposes. The addictive potential of midazolam will be mitigated by using a low dose and a slow infusion paradigm. Midazolam is used very frequently in the pediatric setting, and is not thought to be associated with precipitating subsequent benzodiazepine abuse. The risks will further be mitigated by screening out adolescent subjects with concurrent substance use disorders. Subjects will also be warned about the abuse potential in all consent/assent documents.

**Blood drawing/intravenous placement:** Bruising or thrombosis can occur with placement of the intravenous line. A total of 110cc will be drawn over 4 weeks (30cc at baseline, 35cc on first infusion day (Day 0), 5cc on Day 1, 35cc on second infusion (Day 14), and 5cc on Day 15), which equates to 1.5cc/kg – 2.2cc/kg (based on average weights of 13-17yo adolescents). This amount drawn is considerably less than the 9.5cc/kg over 8-week requirement set by the review board. The risks of blood draws include brief pain at the time of needle insertion, bruising, swelling at needle site and rarely, fainting or infection.

**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 of depression and/or anxiety symptoms or school refusal if applicable 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 CDRS-R and MADRS, and/or PARS and school attendance questionnaire, as well as 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 CDRS-R 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. In the event that a subject is judged to remain significantly depressed and/or at increased risk for suicidality at the end of the study, we will help make appropriate referrals to outpatient providers, intensive outpatient programs or inpatient psychiatric hospitals as clinically indicated. Investigators may continue close monitoring of significantly at risk subjects until such

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referrals are provided and available to the study participant. Participants who have completed the trial must have a CDRS score of less than 50 to be discharged from the study.

**Magnetic Resonance Imaging:** MRI is considered to be among the safest ways to examine the human body. The United States Food and Drug Administration (FDA) has set guidelines for magnet strength and exposure to radiowaves, and we carefully observe those guidelines. Subjects will be watched closely throughout the study. Some youths may feel uncomfortable or even anxious during the MRI. If this happens to a subject, the subject may ask to stop the study at any time and we will take the subject out of the MR scanner. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste in their mouth or feel tingling sensations or muscle twitches. These sensations usually go away quickly but subjects will be encouraged to tell the research staff if the subject experiences such sensations. MRI poses some risks for certain people. If the subject has some metal object(s) inside his or her body, the subject may not be in this study because the strong magnets in the MR scanner might harm him or her. Another risk is a metallic object flying through the air toward the magnet and hitting subjects. To reduce this risk, we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. Nothing metal can be brought into the magnet room at any time. Also, once subjects are in the magnet, the door to the room is closed so that no one from outside inadvertently approaches the magnet. To minimize this risk, the participant will walk through a ferromagnetic detector to ensure he/she does not have any metal objects on his/her body.

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

**Ketamine Administration:** The dose of ketamine established in prior research (0.5 mg/kg over 40 minutes) will be used in this study to minimize risks. The maximum total dose allowed in this study will be 50mg, corresponding to a weight of 100kg. The most common side effects of ketamine are (1) Elevated blood pressure (relatively common, but dose-dependent) breathing rate and pulse rate, (2) Local pain at injection site and temporary rash (rare) 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. 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. A physician from the Yale Pediatric Sedation Service who is credentialed by YNHH for the administration of ketamine will be present for all infusions, with access to rescue equipment. Subjects will be monitored for at least 3 hours following ketamine infusion by Dr. Bloch. A study doctor will be present at all times during the infusion and recovery. In the event, that a research subject has a significant psychiatric event requiring hospitalization, they will be treated on the adolescent unit (LV2) at Yale Psychiatric Hospital (YPH). Emergent medical care would be provided at Yale-New Haven Hospital, the site of infusion.

All participants will be asked not to engage in demanding work for the first 3 days after the ketamine infusion. However, for those with school refusal, they continue with their regular school schedule. If participants develop psychiatric symptoms, we may admit them to the

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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. 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 (203) 745-9921, Yale Investigational Drug Service phone number, regular hours and telephone numbers of their study physician and research support staff (Angeli Landeros-Weisenberger (203) 737-4809), should unpleasant effects occur after the subject has left the testing facility. All participants are contacted 1, 2, 3, 5, 7, 10, 14, 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.

**Midazolam Administration:** The weight-based midazolam dosing established in prior ketamine trials in adults (0.045mg/kg) will be used to minimize risks, as this is considered a very low dose compared to the sedation literature (122). The maximum total dose allowed in this study will be 4.5mg, corresponding to a weight of 100kg. The most common side effects related to midazolam infusions are hiccoughs, nausea, vomiting, coughing, headache, and drowsiness. In younger children, higher midazolam doses have also been associated with a risk for paradoxical disinhibition or agitation. Midazolam has one of the shortest half-lives of all of the benzodiazepines, and thus adverse events relating to the drug typically are not observed more than 30 minutes following drug administration (74). The most serious possible adverse reactions associated with midazolam, which are associated with higher doses than proposed in the study include: (1) substance abuse/dependence, (2) anaphylaxis or other allergic reaction, (3) respiratory depression or arrest, (4) decreases in blood pressure resulting in end organ damage or death. The serious side effects associated with midazolam are rare. In order to minimize the risk of these side effects, subjects will be medically screened prior to enrollment in the study, vitals will be monitored regularly throughout the infusions (with continuous pulse oximetry), and regularly for the hour following the infusion. To additionally minimize the risks associated with midazolam, a physician from the Yale Pediatric Sedation service will pre-screen subjects and

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will be present for the duration of the infusion, with access to airway equipment (although we believe that the likelihood of a serious event at the dose proposed in this study is low). There will also be access to flumazenil, a reversal agent that rapidly terminates that action of midazolam. The Yale Pediatric Sedation team is credentialed to administer these medications at YNH and have vast experience with midazolam given its common usage, and their consultation has been integral to designing the monitoring parameters detailed herein. Subjects will be monitored for at least 3 hours following ketamine infusion by Dr. Bloch. A study doctor will be present at all times during the infusion and recovery. In the event, that a research subject has a significant psychiatric event requiring hospitalization, they will be treated on the adolescent unit (LV2) at Yale Psychiatric Hospital (YPH). Emergent medical care would be provided at Yale-New Haven Hospital, the site of infusion.

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 (203) 745-9921, Yale Investigational Drug Service phone number, and regular hours and telephone numbers of their study physician and research support staff (Angeli Landeros-Weisenberger, MD (203) 737-5104), should unpleasant effects occur after the subject has left the testing facility. All participants are contacted 1, 2, 3, 5, 7, 10, 14, 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. Numbing spray and distraction techniques will be offered prior to offset the discomfort of iv placement, as is commonly done in Pediatric medical settings. During the infusion days, blood draws will occur off of the non-infusing iv in order to prevent the discomfort of repeated needle sticks. The total amount of blood to be collected in this study is 110cc over 4 weeks (30cc screening + 35cc first infusion day (Day 0) + 5cc on Day 1 + 35cc second infusion day (Day 14) + 5cc on Day 15). This amount ranges from 2.4cc/kg for a 45kg adolescent to 1.7cc/kg for a 65kg adolescent (weight range of 45kg – 65kg for 13-17yo girls and boys). This amount is well below the maximum of 9.5cc/kg over 8 weeks.

**Psychiatric evaluation, rating scales, and questionnaires:** In order to minimize risks associated with the psychiatric ratings and ensure the accuracy of reporting, these measures will be administered by trained research staff and supervised by a study physician. Participants will be informed that they do not need to answer any question on the rating scales or questionnaires that make them feel uncomfortable. Participants will also be informed they can take a break if they become tired from any of the questions or ratings.

**Clinical deterioration:** If a participant shows significant worsening of symptoms, he or she will be removed from the study and 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



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treatment at the Yale Child Study Center or Yale New Haven Hospital, or to receive treatment on a private basis from a referring clinician. In the event that a subject is judged to remain significantly depressed and/or at increased risk for suicidality at the end of the study, we will help make appropriate referrals to outpatient providers, intensive outpatient programs or inpatient psychiatric hospitals as clinically indicated. Investigators may continue close monitoring of significantly at risk subjects until such referrals are provided and available to the study participant. Participants who have completed the trial must have a CDRS score of less than 50 to be discharged from the study.

**Magnetic Resonance Imaging:** In addition to what was stated above, the following steps will be taken to minimize potential risks associated with MRI data collection:

*1) Claustrophobia*

The subjects can be given the option to acclimate to MR imaging by using the mock scanner. In the scanner, subjects will have a mirror with which to view console and room. There will be constant assessment as to how subject is feeling via console speaker. Subjects can have a member of the research team sit in scan room during the study. We will talk with the subject, assess their condition, and ask whether or not they would like to continue. Subjects will be encouraged to relax, will be reassured that they are safe, and we will ask them to use the mirror, music or have someone in the room with them. They will be taken out of the scanner and their scanning terminated if they do not want to continue.

*2) Hearing damage due to loud noises produced by the scanner*

Hearing damage will be minimized by ear plugs and headphones. The ear plugs and headphones are estimated to each reduce noise by approximately 35 db at the sound frequencies generated by the scanner. We will evaluate the fit of the ear plugs and the headphone. This is usually very successful in dampening noise. The subject will be taken out of the scanner and their scanning terminated if they do not want to continue.

*3) Dizziness*

Dizziness will be minimized by sliding the subject slowly into and out of the scanner (dizziness occurs mainly when sliding in and out of scanner). Subjects will be informed the best approach to minimize dizziness is not to clasp one's hands together and not to cross one's legs during scanning. We will tell the subjects they might have dizziness as we position them into the scanner but that it subsides after they are in position. If the dizziness continues, we will take the subject out of the scanner and have them lie supine on the scanner bed until the dizziness passes. Their scanning will be terminated if they do not want to continue.

This MR study is for research purposes only and is not in any way a clinical scan to diagnose diseases for subjects. The scans in this study are not designed for diagnosis. The research team, the MR technologist, and the Magnetic Resonance Research Center are not qualified to interpret the MR scans and cannot give the subject, the subject's parents and/or guardians, or their doctor a diagnostic evaluation of the images. If we see something on a subject's scan that might be medically significant, we will ask a radiologist or another physician to review the relevant images. If that person recommends that a subject should seek medical advice, then the primary investigator or consulting physician will contact the subject's parent and/or guardian, about the situation, and recommend that the family seeks medical advice as a precautionary measure. At that point, the decision to seek advice or treatment is completely up to the parent/guardian, and their child's doctor. If the child's doctor wants to pursue additional MR images, the research scans from this study will not be available, and new scans that are appropriate for medical diagnosis will need to be done. While there are no known risks associated with MRI and pregnancy it is standard clinical practice to avoid MRI scans in pregnancy when possible and therefore there is not a large pool of data. Given this, pregnant subjects will be excluded from study. Scanning is performed on the campus of the Yale

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Medical Center so that emergency medical intervention is available in the event of an adverse event.

Dr. Blumberg has extensive experience in performing scans with young people particularly including those with anxiety and associated problems. Minimizing head movement is critical especially when scanning children and adolescents. We are careful both to comfortably stabilize head position for the subject with use of foam padding and velcro straps, and to be sure at least one staff member whom the subject has gotten to know during the interview process stays during scanning to support the subject through the scanning session and to provide reminders about remaining still, which has helped keep the motion in our data minimal. This has been further enhanced by the outstanding technical staff members at the MRRC, who have many years of experience in clinical research studies and are highly supportive and skilled in working with our research subjects. In over Dr. Blumberg's 16 years of MRI research at the MRRC, it has been rare that we need to remove a subject from the scanner due to anxiety. However, if this issue should arise we have the ability to utilize the mock scanner that is in a room down the hall from the scanner and resembles an actual scanner.

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

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

We judge this study to be moderate risk, but with the possibility of direct benefit to the pediatric patient.

- b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study?

We judge this study to fall into the following Pediatric risk category:

45 CFR 46.405: Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects

20 CFR 50.52: Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects

Ketamine arm: Given the efficacy of ketamine as a rapidly-acting antidepressant and anxiolytic in adults, ketamine also may alleviate symptoms of depression and anxiety in adolescents.

Midazolam arm: Midazolam has been previously used for short-term anxiolysis in both children and adults so it may reduce anxiety symptoms temporarily (for minutes to hours). While the active control medication is not expected to alleviate symptoms of depression or anxiety over the longer term, the high level of contact with Pediatric Psychiatry (scheduled contact 7 out of the 14 days post-infusion), as well as 24/7 access to Child Psychiatry may directly benefit the subjects.

- c. Copy and 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

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iii. High risk

**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 reapproval of the protocol is sought). During the review process, the principal investigator 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 greater than minimal for the following reasons:** (choose those that apply)

1. We do not view the risks associated with the ketamine and midazolam infusions as minimal risks.
2. Given the established safety and validity of the current ketamine dosing from our prior work in adults, as well as the frequent use of both ketamine and midazolam at higher doses in pediatric populations, we do not view the proposed studies as high risk.

Although we have assessed the proposed study as one of greater than minimal 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 (Dr. Michael Bloch) 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:**

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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 results in any of the following outcomes:

1. Death;
2. A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3. A persistent or significant disability or incapacity;
4. A congenital anomaly or birth defect; OR
5. Any other adverse event that, 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.

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 UPIRSOs (including Adverse Events) to the IRB

The principal investigator will report the following types of events to the IRB:

Any incident, experience or outcome that meets ALL 3 of the following criteria:

1. Is unexpected (in terms of nature, specificity, severity, or frequency) given (a) the research procedures described in the protocol-related documents, such as the IRB-approved protocol and informed consent document and (b) the characteristics of the subject population being studied; AND
2. Is related or possibly related to participation in the research (*possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); AND
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, legal, or social harm) than was previously known or recognized.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) may be medical or non-medical in nature, and include – but are not limited to – *serious, unexpected, and related adverse events* and *unanticipated adverse device effects*. **Please note** that adverse events are reportable to the IRB as UPIRSOs **only** if they meet all 3 criteria listed above.

These UPIRSOs/SAEs will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website. All related events involving risk but not meeting the *prompt* reporting requirements described in IRB Policy 710 should be reported to the IRB in summary form at the time of continuing review. If appropriate, such summary may be a simple brief statement that events have occurred at the expected frequency and level of severity as previously documented. In lieu of a summary of external events, a current DSMB report can be submitted for research studies that are subject to oversight by a DSMB (or other monitoring entity that is monitoring the study on behalf of an industry sponsor).

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**7. Plan for reporting adverse events to co-investigators on the study, as appropriate the protocol's research monitor(s), e.g., industrial sponsor, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), Protocol Review Committee (PRC), DSMBs, study sponsors, 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):

All Co-Investigators listed on the protocol.

Food and Drug Administration

The principal investigator (Dr. Michael Bloch) 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.

MDD Arm: Controlled studies of ketamine (both saline and midazolam controls) in adult MDD report effect sizes of 1.5 (34, 132). If of similar efficacy in adolescents, a sample size of 18 would have power greater than 0.8 to detect a difference from midazolam ( $\alpha=0.05$ ) for an effect size  $\geq 1.0$ . For the primary outcome, paired t-tests will compare MADRS score at 1 day following infusion between midazolam and ketamine. Scores of the other rating scales and time course will be assessed as secondary measures. It is quite possible that the benefits of ketamine will be smaller in adolescent depression compared to adult 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 midazolam) during the first week following infusion as sufficient evidence towards conducting a more definitive trial. Treatment response for the MDD cohort is defined as 40% reduction in CDRS-R scores anytime in the first three days following infusion.

Anxiety Arm: Controlled studies of ketamine (saline controls) in adult MDD assessing anxiety as a secondary outcome have reported effect sizes of 1.4 at day 1. Similarly, controlled studies of adults with OCD and PTSD both reported an  $ES \approx 0.9$  at day 1 following infusion (96, 98). By comparison, in our adult social anxiety trial we observed an  $ES \approx 0.8$  at day-1 following infusion on the CGI. Given a sample size of 18 adolescents we would have power greater than 0.8 to detect a difference from midazolam ( $\alpha=0.05$ ) for an effect size  $\geq 1.0$ . For the primary outcome, paired t-tests will compare MASC physical symptom subscale score at 1 day following infusion between midazolam and ketamine. Scores of the other rating scales and time course will be assessed as secondary measures. It is quite possible that the benefits of ketamine will be smaller in adolescent anxiety compared to previous adult trials. We would define treatment response as a  $CGI \leq 3$  and a

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greater than 35% improvement in the MASC physical symptoms subscale at any time point during the first 7 days following infusion. The MASC physical symptoms was chosen as the primary outcome for the anxiety disorders arm of this trial because (1) we believe the physical symptoms of anxiety may change within a short time frame (e.g. 1 -day) whereas the behavioral symptoms of anxiety (avoidance, performance fears, social anxiety symptoms, fear of humiliation/rejection symptoms) are less likely to be detectable over short time periods.

<b>SECTION VI: RESEARCH INVOLVING DRUGS, BIOLOGICS, PLACEBOS AND DEVICES</b>
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**A. DRUGS and BIOLOGICS**

1. **Identification of Drug or Biologic:** What is (are) the **name(s)** of the drug(s) or biologic(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 Dr. Bloch holds a therapeutic license for administering controlled substances.

Midazolam HCl (Versed) is FDA approved in children and adolescents for sedation, and is often used as an anxiolytic agent prior to induction of general anesthesia with other anesthetic agents, or as a sole sedating agent for minor procedures. As with ketamine, Dr. Bloch holds a therapeutic license for administering controlled substances.

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

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

Who holds the IND?

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

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(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:

2. 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
3. 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
4. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.  Yes  No

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

- i. The clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following (check all that apply):
- Blood grouping serum
  - Reagent red blood cells
  - Anti-human globulin
- ii. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and
- iii. The diagnostic test is shipped in compliance with 21 CFR §312.160.

**Exempt Category 3**

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

**Exempt Category 4**

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

5. **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:** Ketamine has a wide margin of safety, and is usually given in doses of 1mg/kg –

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4.5mg/kg IV over 60 seconds when used a sole anesthetic agent. It has been used routinely in pediatrics for over 40 years, typically at higher doses than proposed in the current study. Ketamine has been used to treat treatment-refractory depression in adults at Yale for over 20 years, with robust evidence for medical and psychiatric safety (see Preliminary Data).

There are several potential risks associated with ketamine use. These include **1) Cardiovascular:** elevated blood pressure and pulse rate (relatively common and are dose-dependent) and very rare changes in cardiac rhythm. **2) Respiration:** respiratory rate is frequently elevated; however, with high dose administration severe respiratory depression and apnea have been reported (<1.5% of transient apneic events at anesthetic doses in pediatric emergency room settings (133). Ketamine also has rarely been associated with laryngospasm. **3) Eyes:** ketamine has been associated with slight elevations in intraocular pressure. **4) Gastrointestinal:** Anorexia, nausea and vomiting have been observed, however this is usually not severe. Vomiting has been seen in <4% of children in emergency room sedation settings (133). **5) Neurological:** enhanced skeletal-muscular tone resulting in tonic clonic movements have rarely been observed with acute administration. **6) General:** Anaphylaxis, local pain at injection site and transient rash have been described at the case report level. **7) Psychological:** ketamine has been associated with a variety of transient symptoms including, but not limited to anxiety, dysphoria, disorientation, insomnia, flashbacks, hallucinations, and psychotic episodes. Emergence reactions have occurred in approximately 12% of subjects given anesthetic doses of ketamine. These symptoms usually last no more than a few hours. However, recurrences have taken place up to 24 hours after the anesthetic dose administration. Recovery agitation after ketamine iv sedation in the pediatric emergency room has been seen in <1.5% of children (133). It is also believed that the incidence of the psychological disturbances is reduced with the use of lower doses. No residual adverse psychological effects are known to have resulted from the medical use of ketamine. **8) Substance abuse/dependence:** Ketamine has been reported as a drug of abuse. Reports suggest that Ketamine dependence and tolerance are possible following prolonged administration. A withdrawal syndrome with psychotic features has been described following discontinuation of long-term ketamine use. Therefore, ketamine should be prescribed and administered with caution. It is unclear whether exposure to ketamine in the laboratory can result in ketamine use or abuse. All participants are encouraged not to participate if they have concerns about the possibility of ketamine abuse. Also, they are asked to contact us immediately if they become aware of a desire to use or abuse ketamine. All participants are advised that we would refer them to an appropriate treatment facility if necessary. In our experience doing research with ketamine, we are unaware of individuals abusing ketamine as a result of study participation.

**Midazolam:** Midazolam is used frequently in the pediatric emergency room and in sedation settings, either as a sole agent for anxiolysis, or in combination with other sedatives and anesthetics for more complex or prolonged procedures. It is typically given at doses of 0.5-0.5mg/kg over 2 minutes, depending on the intended level of sedation (mild versus deep sedation). It has been used routinely in Pediatrics since the 1990's, typically at higher doses than those described in this study.

There are several potential risks associated with midazolam use: **1) Cardiovascular:** decrease in blood pressure (hypotension in <3% of pediatrics patients at sedation dosing ref) and very rarely, changes in cardiac rhythm. **2) Respiration:** apnea, cough, hiccups, decreased tidal volume and respiratory rate (transient apnea has been reported in <3% of pediatric patients at sedation dosing); with high dose administration severe respiratory depression, airway obstructions, apnea,



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and respiratory arrest have been reported. **3) Eyes:** may cause nystagmus **4) Gastrointestinal:** can be associated with nausea and vomiting (<3% of adult patients). **5) Neurological:** may cause drowsiness, headache, oversedation; like all benzodiazepines, midazolam has amnestic properties, more notable as dose increases **6) General:** Anaphylaxis, local pain at injection site and transient rash have been reported. **7) Psychological:** midazolam can be associated with paradoxical agitation (particularly in the elderly or in very young children), however is estimated at <1% of patients; there are also rare reports of emergence delirium, euphoria, and hallucinations, although these are associated with higher dosing than proposed here. Additionally, fast-acting reversal medications are available (flumazenil) that can terminate midazolam's effects should the patient experience side effects during the infusion. **8) Substance abuse/dependence:** As with all benzodiazepines, physical and psychological dependence is associated with prolonged use. The single infusion proposed in the study is not expected to produce any physiological dependence. As all benzodiazepines have some abuse potential, midazolam should be prescribed and administered with caution. Midazolam is used frequently in pediatric medical settings, at higher doses administered over shorter periods of time, and this use has not been linked with subsequent addiction problems. That said, all participants are encouraged not to participate if they have concerns about the possibility of midazolam abuse. Also, they are asked to contact us immediately if they become aware of a desire to use or abuse midazolam. All participants are advised that we would refer them to an appropriate treatment facility if necessary.

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

Ketamine (Ketalar) and midazolam (Versed) will be obtained from the YNHH Research Pharmacy

b) Is the drug provided free of charge?  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 the 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 YNHH research pharmacy, and will be picked up by investigators on the morning of infusion.

Midazolam is chemically designated as HCl is 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo [1,5-a] [1,4] benzodiazepine hydrochloride. It is formulated as a slightly acidic sterile solution for intravenous injection. It is available in both preservative and preservative-free preparations, and is available in 1mg/mL and 5mg/mL preparations. The medication will be obtained and stored at the YNHH research pharmacy, and will be picked up by investigators the morning of the infusion.

Check applicable Investigational Drug Service utilized:

YNHH IDS

CMHC Pharmacy

Yale Cancer Center

West Haven VA

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 PET Center 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**

Provide a justification which addresses the following:

a. Describe the safety and efficacy of other available therapies (if any). Standard treatments for depression and anxiety in adolescents include SSRIs, SNRIs, and psychotherapy. Nearly 40% of pediatric patients fail to respond to these first line pharmacotherapies and of those non-responders, nearly half remain depressed and anxious after switching medications and adding psychotherapy. Even when effective these medications take several weeks to take clinical effect, leaving a vulnerable period between the initiation of treatment and the start of resolution of symptoms of anxiety and depression. Importantly, these medications carry a black box warning for Pediatric patients as they are associated with a small, but significant increase in suicidality. Psychotherapy does not carry any specific medical or psychiatric risks, and subjects enrolled in the study are permitted to continue to engage in psychotherapy if they have already been doing so. They are also permitted to stay on their current pharmacotherapies during the 4-week trial, but are not allowed to make medication changes.

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

One dose of IV midazolam will be given. However, the protocol will require 2 weeks in between each infusion. During this time the participant would not be receiving any additional treatments (they may remain on any current therapy (daily medications, psychotherapy, etc.)).

c. Address the greatest potential harm that may come to a participant as a result of not receiving effective therapy (immediate or delayed onset.)

Symptoms of MDD, anxiety and common comorbid 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. The crossover design also ensures that all subjects will receive the active medication within the month of the study protocol. 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 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?

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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.

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.

This study is designed to determine the short-term safety and benefit of ketamine as a rapidly acting antidepressant and anxiolytic in adolescents. Further studies will be needed to carefully assess the safety and efficacy of a longer-term treatment course with this medication.

**B. DEVICES - N/A**

**SECTION VII: RECRUITMENT/CONSENT/ ASSENT**

**1. Targeted Enrollment:** Give the number of subjects: 18

- 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\_N/A\_\_

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

- |   |  |                                     |
|---|--|-------------------------------------|
| <input checked="" type="checkbox"/> Flyers                          | <input checked="" type="checkbox"/> Internet/Web Postings                                      | <input type="checkbox"/> Radio      |
| <input type="checkbox"/> Posters                                    | <input checked="" type="checkbox"/> Mass E-mail Solicitation                                   | <input type="checkbox"/> Telephone  |
| <input checked="" type="checkbox"/> Letter                          | <input checked="" type="checkbox"/> Departmental/Center Website                                | <input type="checkbox"/> Television |
| <input type="checkbox"/> Medical Record Review                      | <input checked="" type="checkbox"/> Departmental/Center Research Boards                        | <input type="checkbox"/> Newspaper  |
| <input checked="" type="checkbox"/> Departmental/Center Newsletters | <input checked="" type="checkbox"/> Web-Based Clinical Trial Registries                        |                                     |
| <input checked="" type="checkbox"/> YCCI Recruitment Database       | <input checked="" type="checkbox"/> Clinicaltrials.gov Registry (do not send materials to HIC) |                                     |
| <input type="checkbox"/> Other (describe):                          |  |                                     |

**3. Recruitment Procedures:**

- a. Describe how potential subjects will be identified. Subjects will be identified through their response to the contact number on the clinicaltrials.gov listing, flyers, internet ads, or postings on the departmental website/YCCI recruitment database. We will also reach out to local child mental health providers in the area, who may tell their patients about this study.

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- b. Describe how potential subjects are contacted. 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? The study investigator and listed research staff will be recruiting potential subjects.

**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 any health information 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:

## 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

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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 word of mouth, clinicaltrials.gov, physician referrals, and Internet ads. 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 advertisements or 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. **Jennifer Dwyer, MD, PhD, Amalia Londono Tobon, MD, Angeli Landeros-Weisenberger MD, Michael H. Bloch MD, MS; Jessica Johnson BS.**

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.

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Subjects will be minors (ages 13-17) and the consents will be obtained from the parent (guardians). We will also obtain assent from minors participating in our trial. Trained research study staff or the principle investigator will review the consent documents verbally with both the parent and child. Assent will be signed in the presence of the child's parent/guardian.

10. **Evaluation 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.

Subjects will be minors (ages 13-17) and the consents will be obtained from the parent (guardians). We will also obtain assent from minors participating in our trial. Trained research study staff or the principle investigator will review the consent documents verbally with both the parent and child. Assent will be signed in the presence of the child's parent/guardian. A brief questionnaire will be used to assess their basic understanding of our protocol – random order, need for regular visits, and risks of ketamine. If for any reason, it becomes clear that either the parent or child cannot comprehend trial design or procedures they will not be enrolled in this study.

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.

Compound Authorization and Parental Permission Form and adolescent assent form (ages 13-17).

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.

This protocol will not involve Non-English speaking subjects due to an inability to adequately translate the consent materials and clinical rating and the investigator and study staff's non-fluency in languages other than English.

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)**

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

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

a. Would the signed consent form be the only record linking the subject and the research?

Yes  No

b. Does a breach of confidentiality constitute the principal risk to subjects?

Yes  No

**OR**

c. Does the research activity pose greater than minimal risk?

Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note:

Recruitment/screening is generally a minimal risk research activity.

No

**AND**

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

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

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

a. Would the signed consent form be the only record linking the subject and the research?

Yes  No

b. Does a breach of confidentiality constitute the principal risk to subjects?

Yes  No

**OR**

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

**AND**

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

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

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

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

Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note:

Recruitment/screening is generally a minimal risk research activity

No

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

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

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

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

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

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- 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?

<b>SECTION VIII: PROTECTION OF RESEARCH SUBJECTS</b>
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**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?
- b. How will the research data be collected, recorded and stored?
- c. How will the digital data be stored?  CD  DVD  Flash Drive  Portable Hard Drive  Secured Server  Laptop Computer  Desktop Computer  Other
- d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?  
Do all portable devices contain encryption software?  Yes  No
- 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.
- 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)
- g. If appropriate, has a [Certificate of Confidentiality](#) been obtained?
- 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.

(a) Private identifiable information will be collected (name, date of birth, age, telephone number, address, medical and psychiatric history, diagnoses, laboratory tests, and psychiatric rating scores) but will be kept confidential and will not be divulged in any publication emanating from this work. The urine toxicology results will be placed in the research study record.

A Certificate of Confidentiality has been obtained by the investigator to protect all sensitive information connected with this study.

(b) Clinical data, outcomes of diagnostic instruments, and research data will be collected by the principal investigator and other study personnel and stored in a locked file cabinet in a locked office. Data will be entered into a database on a password-protected computer in a locked office, by study personnel. 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



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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. 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) Above

(d) All data obtained from subjects will be coded and stored in locked cabinets/password protected computer in an office that is locked to ensure confidentiality. 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.

(e) 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.

(f) In addition to the study investigators, co-investigators, and study staff, members of HIC and the study sponsor may have access to the study data.

(g) 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 YNHH 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) Yes. Evidence of child abuse or situations in which the subject is deemed a danger to self or others will be reported.

## SECTION IX: POTENTIAL BENEFITS

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

Ketamine arm: While there may be no direct benefit from a subject’s participation in this study, the success of ketamine as a rapid-acting antidepressant in adult patients suggest that adolescent subjects may receive a significant benefit. Given the crossover design, all subjects will be exposed to the potentially beneficial intervention. The potential benefits to society of these investigations are considerable. Depression and anxiety continue to be a major public health

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problem with tragic cost to the individual, the family, and the community. The present study may improve our understanding of depression, anxiety and SRB by providing a pharmacologic rationale for developing novel treatments.

Midazolam arm: While the active control medication is not expected to significantly relieve depressive symptoms, the high frequency of contact with a child psychiatrist and research staff may provide a benefit to subjects. Patients will have schedule contact with Child Psychiatry on Days 1 (in person), 2, 3, 5, 7 (in person), 10, and 14 (in person) after the infusion, and will have 24/7 access to a Child Psychiatrist for any patient-initiated contact. Midazolam is a benzodiazepine that is also utilized to ameliorate anxiety symptoms in many patients.

## SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

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

The subject and his/her parent/guardian may discuss other non-research treatments for MDD and/or anxiety and/or SRB with their practitioner or continue with their current stand of care. Other treatment alternatives include: change to another class of antidepressants (e.g. selective norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs). Monoamine uptake inhibitors (MAOIs), psychotherapy (e.g. cognitive behavioral therapy, insight-oriented psychotherapy).

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.

Subjects will be paid \$375 if they complete all scheduled visits.

If they leave the study early, they will be compensated \$10 for each completed in-person study visit (6 total), \$5 for each telephone study assessment (8 total). Additionally, participants will be paid \$25 for each of the infusion days (2 total). Subjects will be paid \$50 for each MRI and \$25 for each neuropsychological assessment (Baseline and 24 hours after each infusions) (3 Total each.).

Participants will receive an additional \$75 if they complete all assessments for SRB.

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 drug and all medical treatment in this research study will be provided free of charge. There will be no charges for study visits. Costs of the participant are thus limited to the cost of transportation to and from the study appointments and their time spent participating in the study.

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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 provide 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 treated at Yale New Haven Hospital (the location of the infusion). Should there be adverse psychiatric effects as a result of the study they will receive inpatient treatment by going through the Yale New Haven Hospital Psychiatric 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.

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

In the unlikely event that any psychiatric care more intensive than regular clinic visits is required as a direct result of participation in this study, study personnel will provide emergent care and stabilization. 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 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. These costs include emergency care for side-effects of ketamine and psychiatric treatment for worsening of depression and anxiety symptoms that may occur during the course of the trial.

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 depressive 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 depressive symptoms as a result of the protocol.

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