Randomized Controlled Trial of Repeated-Dose Intravenous Ketamine for PTSD

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Mount Sinai	Protocol Title:	Randomized Controlled Trial of Repeated-Dose Intravenous Ketamine for PTSD
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MSSM Protocol Template

Instructions:

1. *Prepare a document with the following sections. Note that, depending on the nature of your research, certain sections below may not be applicable. Indicate N/A as appropriate, explaining where possible.*
2. *For any items described in the sponsor's protocol, grant application or other source documents submitted with the application, you may reference the title and page numbers of these documents rather than cutting and pasting into this document.* ***Do NOT refer to any derived documents, such as the Sample Consent document, or other internal documents required with the submission.***
3. *If you reference page numbers, attach those pages to this protocol.*
4. *When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.*

1) Objectives

The objective of the present research protocol, a parallel-arm, double-blind, randomized controlled clinical trial, is to test the efficacy of repeated intravenous administration of the glutamatergic NMDA receptor antagonist ketamine in providing (1) rapid relief of and (2) sustained improvement in core PTSD symptoms and co-morbid depressive symptoms in patients with chronic PTSD. The effects of ketamine will be compared with those of repeated intravenous administration of the benzodiazepine anesthetic midazolam, which mimics some of the acute subjective effects of ketamine but is expected to have lesser or less sustained anxiolytic effect, and no sustained antidepressant effect. Patients with chronic PTSD will be randomized to receive repeated intravenous administrations of either ketamine or midazolam, administered 3 times a week over the course of 2 consecutive weeks.

We have completed a randomized, double-blind controlled study of a single dose of IV ketamine (compared to a single dose of IV midazolam) for chronic posttraumatic stress disorder (PTSD) at the Depression and Anxiety Center (DAC) at Mount Sinai. In that study, we found ketamine infusion to be associated with significant and rapid improvement in PTSD symptom severity, compared to midazolam, when assessed 24 hours post-infusion (Feder et al., 2014). Ketamine was also associated with improvement in co-morbid depressive symptoms and in overall clinical presentation, and was generally well-tolerated without clinically significant persistent dissociative symptoms.

In the past ten years, evidence has emerged showing that sub anesthetic doses of ketamine (0.5mg/kg) administered over a 40-minute infusion period can have a fast-acting antidepressant effect on both treatment-naïve and treatment resistant depression (TRD) individuals (Murrough et al., 2013; Fond et al., 2014; McGirr et al., 2014). We also reported results from an open-label study of IV ketamine administration that was conducted at DAC in patients with TRD, which showed a more prolonged improvement in depressive symptoms in this population (aan het Rot et al., 2010). Given the initial promising findings in patients with chronic PTSD summarized above (Feder et al., 2014), as well as our experience and findings with ketamine in patients with TRD (Berman et al., 2000; Zarate et al., 2006, aan het Rot et al., 2010; Murrough and Charney, 2010; Murrough et al., 2013), it is now imperative to identify strategies for effective and practical continuation pharmacotherapy for patients with chronic PTSD.

SPECIFIC AIMS

Aim 1: To examine the effect of repeated intravenous administration of ketamine on core PTSD symptoms in patients with chronic PTSD. **Hypothesis:** Repeated intravenous administration of ketamine will be effective in (1) rapidly reducing core PTSD symptoms and (2) maintaining improvement in core PTSD symptoms, measured over time, compared to repeated intravenous administration of midazolam.

Aim 2: To examine the effect of repeated intravenous administration of ketamine on co-morbid depressive symptoms in patients with chronic PTSD. **Hypothesis:** Repeated intravenous administration of ketamine will be effective in (1) rapidly reducing co-morbid depressive symptoms and (2) maintaining improvement in co-morbid depressive symptoms, measured over time, compared to repeated intravenous administration of midazolam.

Aim 3: To examine the safety and tolerability of this intervention. **Hypothesis:** Ketamine administered via the intravenous route will be well tolerated, with limited side effects including short-lived dissociative effects.

Aim 4 (Exploratory): To measure the effects of ketamine on emotion-processing networks in the brain, in particular amygdala, insula, ACC and other prefrontal cortex (PFC) regions involved in top-down regulation of emotion processing, including the ventromedial PFC (vmPFC) and other regions.

2) Background

PTSD is a debilitating anxiety disorder characterized by intrusive re-experiences of traumatic events, avoidance of situations and stimuli that serve as reminders of these events, and increased startle and hypervigilance. Patients with PTSD often suffer from co-morbid depressive symptoms, and many have significant memory impairments. Existing drug treatments are unsuccessful in a majority of patients, especially in those with combat-related PTSD.

As summarized above, several studies, including those conducted by our research group, have reported rapid improvement in depressive symptoms following a single IV infusion of sub-anesthetic doses of ketamine in patients with TRD, including a large study comparing ketamine to midazolam (Berman et al., 2003; Zarate et al., 2006; aan het et al., 2010; Murrough and Charney, 2010; Murrough et al., 2013). As mentioned above, we have also reported sustained improvement in depressive symptoms following repeated administration of IV ketamine in patients with treatment-resistant MDD in an open-label trial (aan het Rot et al., 2010), and have recently completed a study of intranasal ketamine administration for treatment-resistant MDD, also showing significant improvement in depressive symptoms (Lapidus et al., 2014). Finally, we have recently completed a randomized cross-over trial of a single IV infusion of ketamine, compared to a single IV infusion of midazolam, in patients with chronic PTSD, demonstrating significant rapid improvement in core PTSD symptoms following ketamine administration, as well as improvement in co-morbid depressive symptoms (Feder et al., 2014).

Thus the effects of ketamine administration on depressive symptoms in patients with TRD are well-established, and we have shown more recently that a single IV infusion of ketamine significantly improved core PTSD symptoms and co-morbid depressive symptoms in our initial, proof-of-concept study in patients with chronic PTSD. The next steps are to: (1) further test the efficacy of ketamine in achieving rapid symptom relief in patients with PTSD; (2) test the efficacy of repeated administration of intravenous ketamine in maintaining symptom relief in patients with PTSD; and (3) examine the safety and tolerability of this intervention in PTSD patients.

In the present study, and consistent with our prior studies, we expect a rapid reduction of core PTSD symptoms after the first intravenous infusion of ketamine. Over the course of subsequent administrations (6 total administrations over 2 weeks), we expect

further and/or sustained reduction in PTSD symptoms, as well as reduction in co-morbid depressive symptoms. We will also examine the tolerability and safety of this intervention.

Functional neuroimaging, PTSD and response to ketamine:

As an exploratory aim, we plan to measure the impact of ketamine on neural emotion processing networks. Functional neuroimaging (functional magnetic resonance imaging - fMRI) studies of patients with PTSD have shown altered reactivity in emotion processing networks, also involved in fear learning and extinction, including the amygdala, insula, vmPFC and dorsal anterior cingulate cortex (dACC), among other regions (Pitman et al., 2012). Tasks involving viewing emotional facial expressions (e.g., fearful, angry, happy) are well-suited to study amygdala reactivity to negative facial expressions compared to neutral or happy expressions, and have been used to study predisposition to anxiety, as well as patients with anxiety disorders or PTSD, including changes in emotion processing networks pre-/post-treatment interventions (Hariri et al., 2002, 2005; Fonzo et al., 2010, Shin et al., 2005, Bryant et al., 2008). We plan to employ emotion processing tasks to study the effects of ketamine infusion (compared to midazolam infusion) in patients with chronic PTSD, by conducting fMRI imaging pre- and post-study drug administration.

3) Setting of the Human Research

All of the human research will be conducted at the Icahn School of Medicine at Mount Sinai. Consent will be obtained at Mt. Sinai premises, prior to a screening interview, with only members of the research group present. These offices are located at the Depression and Anxiety Center (DAC) on the second floor of [redacted], and in the Outpatient Psychiatry Department building located at [redacted], where the office for the PI (Dr. Feder) is located, a few blocks from [redacted]. Drug administration, acute monitoring, and initial assessments will be performed in the Clinical Research Unit (CRU) on the first floor of the Annenberg building or at the Psychiatry Infusion Suite on the 5th floor of the Icahn building. All monitoring and follow-up assessments will be performed at DAC. Functional MRI scans will be completed at the Translational Molecular Imaging Institute (TMII) in the Hess Center for Science and Medicine. No research will be performed outside of Mt. Sinai. No reference to the potential participant's identity will be made outside of closed quarters.

4) Resources Available to Conduct the Human Research

The Icahn School of Medicine at Mount Sinai's DAC (Director James Murrough, MD, Ph.D) actively and regularly recruits patients for clinical trials of interventions for PTSD. In addition, several studies with ketamine have been performed by DAC, and current DAC investigators have conducted NIMH- and DoD-sponsored clinical trials for PTSD and mood disorders. Based on our previous recruitment of patients with PTSD at Mt Sinai, we estimate being able to recruit and successfully enroll on average 1 to 1.2 patients per month with chronic PTSD over a 36- to 48-month period.

DAC is located on the second floor of [redacted], which is part of the Mt. Sinai Medical Center. Available space in DAC includes 8 private offices, 2 treatment rooms, one examination/phlebotomy room, a neuropsychology room, a conference room, and 7 cubicles for research assistants and interns, as well as a comfortable waiting area. The clinic has adequate office space for faculty members, research assistants, and post-doctoral fellows. Additionally, Dr. Feder, a DAC investigator, has an office located at [redacted], a few blocks away from [redacted]. All office space is fully equipped with necessary elements for conducting research, including computers using a common network, printers, telephones, fax machine, photocopy machines, and supplies.

All staff members listed on this protocol have extensive clinical experience, including 5 psychiatrists, 1 PhD in clinical psychology, 1 LMSW-PhD in neuroscience, and several research coordinators. All listed Mt. Sinai faculty members have extensive research experience and are familiar with performing research at Mount Sinai. No research will be performed outside Mt. Sinai for this project. All staff participating in this study will be fully informed about the protocol and their trial-related duties. A Manual of Procedures (MOP) will be designed and accessible to address the general aspects of the study, summarizing the inclusion/exclusion criteria, treatment interventions, assessment tools, and summary of the procedures. All staff who screen and evaluate patients will be trained on scale administration.

After the protocol is described to the participant and the participant's questions are answered, the participant will be asked to summarize the procedures that he/she will undergo and to describe 2 risks involved in the study. An independent psychiatrist will assess the participant to determine whether the study is understood and informed consent can be provided. Only individuals with capacity to consent will participate in this study.

5) Study Design

a) Recruitment Methods

The primary sources of PTSD patients will be self-referrals generated from media advertisements. Print advertisements will be placed in local newspapers (i.e., Village Voice) and college newspapers (NYU, Hunter College). Online advertisements will also be utilized (i.e., Craigslist, Google Search Ad Campaign, Clinical Connection, TrialFacts). Through TrialFacts, we will have targeted advertisements on Google and Facebook. The study will also use online and print advertisements for Veterans' organizations. Additionally, we will advertise on the radio (including, Pandora or Spotify). Participants will also be recruited using paper advertisements, such as flyers, which will be posted in designated areas of Mount Sinai and other college campuses. Flyers will also be posted in designated boards in community areas surrounding Mount Sinai, including, for example, YMCA centers, places of worship and domestic violence shelters with approval from the site. In addition, we plan to recruit participants from clinical practices at Mt. Sinai, including the World Trade Center (WTC) Health Program (and its Mental Health Treatment Program led by Dr. Fatih Ozbay, where the PI, Dr. Feder, is also a staff psychiatrist); Internal Medical Associates (IMA); and the Outpatient Psychiatry Department (OPD); referral of Veterans by clinicians at the James J. Peters and the Manhattan VA Medical centers, as well as Veterans organizations such as Iraq and Afghanistan Veterans of America (IAVA); and also anticipate referrals from other clinicians in the Mount Sinai Medical Center, other New York City area hospitals affiliated with Mount Sinai, and community clinics and programs, who are aware of our clinical and research program. Other sources of recruitment will include outreach at crime victims' treatment programs.

Potential participants who are current or former patients of study investigators (for example, Dr. Feder's patients at the WTC Mental Health Treatment Program) will not be referred directly to the research study. Instead, they will be asked if they would like to participate in the study. Potential participants will be offered an IRB-approved study brochure or flyer that will include information about the study and the contact information of the PI and research coordinator. If the participant is interested, he or she will contact the study team directly. Subjects will be compensated for the time and inconvenience associated with participation in this protocol.

b) Inclusion and Exclusion Criteria

INCLUSION

1. Men or women, 18-70 years of age;
2. Participants must have a level of understanding sufficient to agree to all tests and examinations required by the protocol and must sign a written informed consent document;
3. Participants must fulfill DSM-5 criteria for current civilian or combat-related PTSD, based on clinical assessment by a study psychiatrist and on the CAPS – this is done to ensure at least moderate severity and to safeguard against high placebo response rates;
4. Women must be using a medically accepted reliable means of contraception (if using an oral contraceptive medication, they must also be using a barrier contraceptive) or not be of childbearing potential (i.e., surgically sterile, postmenopausal for at least one year);
5. Women of childbearing potential must have a negative pregnancy test at screening and prior to each intravenous infusion;
6. Participants must be able to identify a family member, physician, or friend (i.e. someone who knows them well) who will participate in a Treatment Contract (and e.g. contact the study physician on their behalf in case manic symptoms or suicidal thoughts develop).

As in our completed study of IV ketamine vs. midazolam for PTSD, we are not excluding patients with co-morbid MDD (except those with bipolar or psychotic depression) because we feel that this will affect the generalizability of our findings. Almost 50% of patients with PTSD have this co-morbid diagnosis. Allowing patients with histories of co-morbid MDD to participate broadens the inclusion criteria to more closely approximate PTSD patients seen in real-world settings. Also, it allows us to investigate the antidepressant effect of ketamine in PTSD patients with co-morbid MDD. In general, inclusion / exclusion criteria are intended to protect patient welfare where, for example, administration of ketamine in the context of standardized research would be inadvisable or unsafe (e.g. because of pregnancy, history of allergy or other intolerance to study drug, or active suicidality). An additional purpose is to limit variability due to demographic and other factors, and to decrease psychiatric co-morbidities that may affect the clinical phenomenology or treatment response and thus obscure findings (e.g. primary diagnosis of bipolar disorder or schizophrenia, co-

morbid substance use disorder).

EXCLUSION

1. Women who plan to become pregnant, are pregnant or are breast-feeding (because the medical risk of using ketamine during pregnancy and breast-feeding is unknown);
2. Serious, unstable medical illnesses such as hepatic, renal, gastroenterologic, respiratory, cardiovascular, endocrinologic, neurologic, immunologic, or hematologic disease, including gastro-esophageal reflux disease, obstructive sleep apnea, history of difficulty with airway management during previous anesthetics, ischemic heart disease and uncontrolled hypertension, and history of severe head injury;
3. Clinically significant abnormal findings of laboratory parameters, physical examination, or ECG;
4. Renal impairment, as reflected by a BUN >20 mg/dL, and/or creatinin clearance of >1.3 mg/dL;
5. Clinically significant hypothyroidism or hyperthyroidism, as indicated by a TSH value 25% above or below the normal range
6. A Body Mass Index (BMI) >40;
7. Patients with uncorrected hypothyroidism or hyperthyroidism;
8. Hormonal treatment (e.g., estrogen) started in the 3 months prior to the first infusion day;
9. History of autism, mental retardation, pervasive developmental disorders, or Tourette's syndrome;
10. History of one or more seizures without a clear and resolved etiology;
11. History of (hypo)mania;
12. Past or current presence of psychotic symptoms, or diagnosis of a lifetime psychotic disorder including schizophrenia or schizoaffective disorder;
13. Drug or alcohol abuse or dependence within the preceding 3 months; a rather narrow time period was chosen, however, in order to allow participation by individuals with a history of substance abuse or dependence problems that could be secondary to their PTSD, and to more closely approximate patients seen in real-world settings; this is the same period of time that we used in our recently completed study of IV ketamine for PTSD.
14. Previous recreational use of ketamine or PCP on more than one occasion; Any recreational use of ketamine or PCP within the last two years will be exclusionary, even if only taken once.
15. Current diagnosis of bulimia nervosa or anorexia nervosa;

16. Diagnosis of schizotypal or antisocial personality disorder (since these are known to reduce the possibility of study completion); other Axis II diagnoses will be allowed;
17. Patients judged clinically to be at serious and imminent suicidal or homicidal risk.
18. A blood pressure of one reading over 160/90 or two separate readings over 140/90 at screen or baseline visits
19. Patients who report current treatment with a long-acting benzodiazepine (e.g., clonazepam, diazepam) or an opioid medication within 2 weeks prior to randomization, and patients who take daily morning doses of any type benzodiazepine. Note: Patients taking stable doses of antidepressant medication or mood stabilizer (such as valproic acid or lithium) for 3 months prior to randomization will be allowed. Patients who report current treatment with a short-acting benzodiazepine (e.g., alprazolam, lorazepam), but not daily in the morning, will be allowed, and will be asked not to take their benzodiazepine on the mornings of infusion days.
20. For subjects who may participate in the MRI portion of the study, claustrophobia, any trauma or surgery which may have left magnetic material in the body, magnetic implants or pacemakers, and inability to lie still for 1 hour or more.

* Potential participants will not be told to discontinue medication for the purposes of this study if there is any evidence that the medication is clinically beneficial. Further, a study physician will not take a potential patient off of a medication; rather, this may only be completed by the prescribing physician. This is our policy across all of our studies.

c) Number of Subjects

We have established our sample size of N = 40 (total number of participants expected to complete study procedures) based on considerations of estimated effect size in parallel-arm, repeated dose, active control design, and feasibility of subject recruitment (please see Data Analysis Plan). Based on our previous recruitment of patients with PTSD at Mt. Sinai, we estimate that we will be able to recruit and successfully enroll on average 1 to 2 patients per month with chronic PTSD, and an average of 1 to 1.2 patients meeting criteria for study drug administration over a 36-month period. Therefore, within a 48-month study period, we expect to complete recruitment, study procedures and data collection.

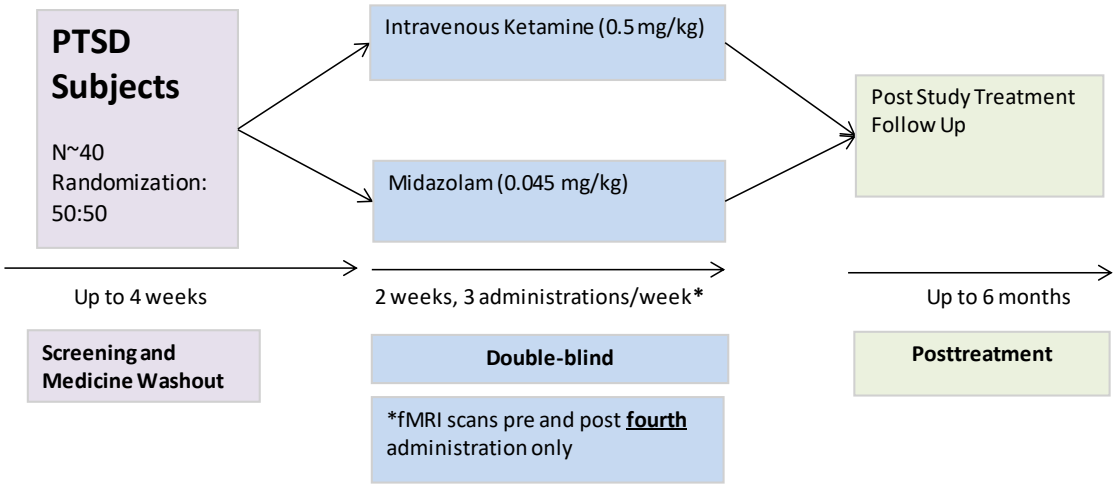
In order to achieve our planned study sample size, based on our prior experience, we expect that up to N = 80 individuals may sign the study consent form.

Rationale for parallel-arm design and three-week subject participation:
We considered both parallel-arm and cross-over randomized, controlled study designs. We concluded that the parallel-arm design is better suited to test a sustained response to continuation dose of IV ketamine in comparison to a control condition, given the potential carry-over treatment effects in treatment responders in a cross-over study design, and has better likelihood to yield meaningful clinical data with a relatively conservative sample size. This conclusion is based on our experience in our recently completed cross-over study of a single IV administration of ketamine compared to a single IV administration of midazolam.

Given that ketamine or midazolam will be administered 3 times per week over 2 weeks, we will employ a parallel-arm design. After 30 study participants have been randomized, partially unblinded analyses (drug A, drug B) will be conducted by a statistician under the supervision of Dr. Emilia Bagiella, a member of the study DSMB, to advise whether to complete the study at that point or continue the study. Other study investigators will remain fully blinded, as the partially unblinded data will be provided directly to Dr. Bagiella by the research pharmacist, Ivy Cohen, Pharm.D.

d) Study Timelines

As detailed in section 5c above, we anticipate that in a 48-month period we will be able to enroll all study participants, complete all study procedures/data collection, and complete a preliminary data analysis. Subject's completion of all study related procedures depends on the length of the screening period and the necessity of a potential washout period. Completion of the study procedures can range from 4 to 8 weeks. The length of the follow-up phase is contingent on the patient's treatment response; formal study follow-up visits will end upon the patient's relapse. The patient follow-up phase can last from one week to six months. Patients who successfully complete the study double-blind phase (6 infusions) will be offered up to three ketamine infusions in an optional open-label extension (open-label phase) if their PTSD symptom levels have not improved during the double-blind phase or if they experience return of symptoms during the Follow-up phase. These three open-label infusions will be administered over the course of up to three weeks.



e) Study Endpoints

The primary outcome is change in PTSD symptom severity measured at 2 weeks after the first infusion, measured with the Clinician-Administered PTSD scale (CAPS) for DSM-5 (Blake et al., 1995; Weathers et al., 1993, 2001).

Secondary outcomes include:

- 24 hours after the first infusion with the Impact of Event Scale - Revised (IES-R) (Weiss and Marmar, 1996).
- Change in PTSD symptom severity at 1 and 2 weeks after the first infusion, measured with the CAPS for DSM-5.
- PTSD symptom severity measured at each drug infusion day with the IES-R
- Depressive symptom severity measured with the Quick Inventory of Depressive Symptomatology - Self-Report (QIDS-SR) and the Montgomery Asberg Depression Rating Scale (MADRS) 24 hours after the first drug administration, with the QIDS-SR at each drug infusion day, and the MADRS at 1 and 2 weeks after the first drug infusion day.
- Treatment-emergent side effects will be measured with the Patient-Rated Inventory of Side Effects (PRISE) at each study session (drug infusion day).
- Functional impairment will be assessed with the Sheehan Disability Scale.
- Additionally, resilience, psychological growth and life satisfaction will be measured with the Connor-Davidson Resilience Scale (CD-RISC), the Purpose

in Life Scale, the abbreviated Medical Outcomes Study (MOS) Social Support Survey, the Posttraumatic Growth Inventory (PTGI) and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).

f) Procedures Involved in the Human Research

The primary objective of this study is to determine the efficacy of repeated administration of intravenous ketamine in achieving rapid improvement in PTSD symptoms and maintaining this improvement over time in patients with chronic PTSD.

Screening and Washout Period:

After receiving complete disclosure about the research and opportunity to fully review the consent form, potential participants will be given the opportunity to ask questions. If they choose to take part in the study, then they will be asked to sign the written informed consent form. Medical and psychiatric history and response to previous treatments will be obtained by a study investigator, and the diagnosis of PTSD will be made using the CAPS for DSM-5 (Blake et al., 1995; Weathers et al., 1993, 2001) The presence of any co-morbid diagnoses will be ascertained with the SCID-P for DMS-5 (First et al., 2001).

At screening, participants will also be administered a battery of cognitive tests to quantify cognitive function at baseline, including tests of processing speed, attention, working memory, learning, and executive function (reasoning and problem solving).

All patients will have a physical examination and specific laboratory tests as outlined in 5). These tests will include: a physical examination, electrocardiogram (ECG), supine and standing vital signs, complete blood cell counts, hepatitis B and C screen, electrolytes, thyroid function tests, fasting blood sugars and chemistries, liver function tests, urinalysis and toxicology screening. A pregnancy test will be performed in premenopausal women. After Screening (which generally takes 2-3 visits), participants are expected to meet all inclusion and not meet any of the exclusion criteria listed above.

Patients who are taking allowed psychotropic medications at Screening (e.g., antidepressant medications) at stable doses for 3 months prior to enrolling in the

study (without changes, including adding or stopping any such medication) will be considered for participation and will be allowed to continue taking these medications. If they qualify for study participation, we will request their permission for a study psychiatrist to contact their prescribing physician for coordinating purposes. The subject's treating physician will oversee the tapering process, if a washout period is necessary. We will also ask that they do not make any changes in dosage of these medications, or start or stop any medication for emotional or psychiatric symptoms, for the duration of the study. If it becomes necessary to change, adjust or stop their psychiatric medication while in this study, we will ask that the participant inform the study PI, Dr. Feder, and this will end the participant's involvement in the study.

If at Screening patients are taking psychotropic medication that is not allowed in the study (e.g., an opioid medication), they must be drug-free for a minimum of 2 weeks prior to Visit 1 (the first IV ketamine or midazolam infusion). Patients who are benefiting from medications that are not permitted in the study will not be tapered off such medications and will be excluded from the study. Patients who experience withdrawal symptoms from the medication taper may have this drug-free period extended. The monitoring of the tapering or "washout" of psychotropic medications will be conducted by the patient's prescribing physician, with consultation from the study physician investigators. Study physician investigators will actively participate in this process only if a patient no longer has an active treatment relationship with her/his prescribing physician.

Participants who qualify and agree to participate in the MRI portion of the study will undergo their first MRI scan at the end of the screening and washout period, the week prior to their first study drug administration.

Study drug infusion days:

Following medical and psychiatric screening, and if required a washout period of 2 weeks from medications that are not permitted in the study (exclusion criteria), eligible patients will be randomized to ketamine or midazolam treatment. Patients who continue to meet symptomatic threshold of severity within 24 hours prior to the first infusion, based on the CAPS, will receive the first IV infusion of 0.5mg/kg of racemic ketamine hydrochloride with an infusion pump over a period of 40 minutes (or IV midazolam (0.045mg/kg with an infusion pump over 40 minutes)). First

infusions will always take place on a Monday, unless there is a holiday or scheduling difficulties that would significantly delay the patient's participation, in which case it will be administered the following day.

After the first infusion of IV ketamine or midazolam, treatment will consist of 5 additional IV ketamine/midazolam infusions conducted on Wednesday, Friday; Monday, Wednesday, and Friday, each preceded and followed by clinical assessments. Participants who tolerate study drug infusion without significant side effects will continue to receive the same maximum total dose. Participants will not receive infusions 3 days in a row.

- The primary outcome measure is the change in PTSD symptom severity measured at 2 weeks after the first infusion, measured with the CAPS for DSM-5.
- Secondary outcome measures include the IES-R, QIDS-SR, CGI-S and CGI-I, administered at visits 1b (24 hours after the first IN administration), 2, 3, 4, 5, 6 (end of week 2), as well as the MADRS, administered at the end of weeks 1 and 2. Additionally, the MADRS will also be administered at 24 hours after the first IV infusion.
- Additional secondary outcome measures will include the Connor-Davidson Resilience Scale (CD-RISC), the Purpose in Life Scale, the abbreviated Medical Outcomes Study (MOS) Social Support Survey, the Posttraumatic Growth Inventory (PTGI) and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), administered at the end of weeks 1 and 2 (in addition to baseline).

Neuroimaging:

Patients randomized to receiving IV ketamine or midazolam, who provide written consent for the MRI portion of the study, will undergo (1) a baseline MRI scan the week prior to the first IV drug infusion, and (2) a second MRI scan approximately one week after the first IV drug infusion.

Scanning Session: We will escort subjects to the Translational Molecular Imaging Institute (TMII) at the Hess Center for Science and Medicine, and ask them to change into a medical gown. Subsequently, an MRI technician will orient and situate patients inside the Siemens MAGNETOM Skyra 3.0 Tesla scanner. The MRI scanner is

without contrast. The MRI portion is optional; subjects will be given this choice during the consent process. Throughout the procedure, participants will remain in contact with an investigator via a microphone and intercom system.

We will record three types of data: functional, structural, and diffusion tensor images. Functional images offer information about changes in blood flow in the brain, a proxy for neuronal activity. Structural images reveal the anatomy of the brain. Diffusion tensor images allow us to probe the integrity of the white matter tracts that connect distant brain regions to one another. During functional imaging, participants will view stimuli consisting of facial expressions of emotion (e.g., fearful, happy) and will press buttons while in the scanner in response to task instructions. The primary endpoint of the MRI portion of the study will be the degree of change observed in emotion-processing networks as a function of ketamine treatment.

After the functional imaging task, we will collect seven additional minutes of functional data. We will instruct participants to keep their eyes open, and to fixate on a small white cross at the center of the scanner computer screen. Next, we will allow participants to close their eyes for twelve minutes while we capture images of their brain structure. The final scan will last seven minutes, recording diffusion tensor data. Total time in the scanner will be approximately 60 minutes.

Visit 1a: First IV Ketamine or Midazolam Infusion

All intravenous infusion procedures and monitoring will take place at the Mount Sinai CRU or the Psychiatry Infusion Suite. Patients will have all procedures performed in a private, quiet room. Initial assessments are performed by the same continuous rater (CR-1) who performed the initial Screening assessment. The CAPS will be administered within 24 hours prior to the first infusion to determine that the participant remains eligible for drug infusion.

A urine toxicology and, for women, pregnancy screen will be performed. In the mornings of treatment days, initial assessments will include the IES-R, QIDS-SR_{16}, HAM-A, Brief Psychiatric Rating Scale (BPRS), Clinician-Administered Dissociative States Scale (CADSS), Sheehan Disability Scale (SDS), Clinical Global Impression scale (CGI), Visual Analogue Scale (VAS), and Profile of Mood States (POMS). At visit 1a (and selected visits listed below), assessments will additionally include the TOP-8, MADRS and CAPS.

Patients will arrive at the CRU on a Monday after an overnight fast for solid food and non-clear liquids. An indwelling catheter will be placed in the antecubital vein of the nondominant arm, and pulse, blood pressure, digital pulse-oximetry, and ECG monitoring will be instituted. All physiologic monitoring data will be recorded on a standard anesthesia record beginning five minutes prior to ketamine infusion. At 9:00 am each patient will receive an intravenous infusion of 0.5mg/kg of ketamine or 0.045mg/kg midazolam over a period of 40 min. Immediately and at 120 minutes following the infusion, patients will be repeatedly assessed by means of clinician-administered and self-report rating scales, including scales to assess side effects. Mood and symptom ratings during and following the administration will be conducted by a separate rater (CR-2). Inter-rater reliability is established for all outcome measures prior to study. Blood will be collected and serum frozen for later testing of ketamine and midazolam levels.

A study physician with privileges to administer ketamine will be present at the infusion throughout the administration of ketamine or midazolam so that potential adverse events can be evaluated and treated promptly, and a medical cart is available for emergencies. The study physician will remain in the continuous presence of the patient following the termination of the ketamine or midazolam infusion or until the patient meets Aldrete criteria (good respiration, O_2 saturation, consciousness, circulation, and activity) for post-anesthesia care, whichever period is longer. After the acute post-infusion period and attainment of sufficient recovery as assessed by the study physician, the patient will be given lunch and will be monitored for two hours from the time of the intravenous infusion. Once the patient has completed the study self-reports and clinical ratings scheduled to begin at +120 minutes, a study physician will evaluate the patient to determine whether he/she can be discharged safely. The earliest time that a patient will be discharged is at +130 minutes (130 minutes after infusion start, i.e., 90 minutes after infusion end), consistent with current clinical practice for patients post-anesthesia. All patients will be asked to have a family member or friend drive them home, or accompany them home by taxi or public transportation, or will be offered car service to get home. Patients will be instructed not to take public transportation on his/her own on the day of discharge from the CRU or Psychiatry Infusion Suite. If the study psychiatrist identifies the presence of any significant psychotomimetic or other problematic side effects, the patient will be kept longer until he/she is ready to be discharged (e.g., awake and alert), as determined by the study physician.. If there is additional need for monitoring after 5:00 pm, the patient will be admitted to the Mount Sinai ED, after which he/she will be exited from the study.

Visit 1b (24 Hours Post First Ketamine or Midazolam Infusion)

Patients will come to DAC (1399 Park). They will be assessed by the same rater who conducted the ratings prior to IV infusion (CR-1), and will complete all assessment scales administered at Visit 1a, with the exception of the CAPS, which will be administered weekly.

Participants who participate in the MRI portion of the study will undergo their second MRI scan during this visit. Patients will also repeat the cognitive testing battery performed at baseline.

Visit 2 (48 Hours Post First Ketamine or Midazolam Infusion)

On Visit 2, patients will go to the CRU for their 2nd IV drug infusion. Initial assessments will include the IES-R, QIDS-SR_{16}, HAM-A, Brief Psychiatric Rating Scale (BPRS), Clinician-Administered Dissociative States Scale (CADSS), Sheehan Disability Scale (SDS), Clinical Global Impression scale (CGI), Visual Analogue Scale (VAS), and Profile of Mood States (POMS).

Participants in this study will receive ketamine or midazolam under blinded conditions. Procedures to be followed **at the CRU** before, during, and after each infusion will be identical to those used during Visit 1a. Clinical ratings ***prior*** to each IV infusion will be obtained by the same rater who evaluated the patient prior to the first IV infusion (**CR-1**). Ratings conducted on IV infusion days ***during and after*** IV ketamine or midazolam infusion will be administered by the same rater who administers ratings on all study days *after* IV ketamine or midazolam infusion (**CR-2**). It is expected that no significant psychotomimetic side effects will occur, such that patients can be discharged at 130 minutes post-infusion. As described above, patients will be assessed by a study psychiatrist at 130 post-infusion to determine if they can be discharged safely. Prior to discharge, all patients will be asked to have a family member or friend drive them home, or accompany them in a taxi or public transportation, or will be offered a car service to get home.

Visits 3-6

Since Visits 1a and 2 will take place on a Monday and Wednesday, respectively, Visits 3-6 will take place on the following Friday; Monday, Wednesday, and Friday. In the event of a Monday holiday, IV infusion of ketamine or midazolam will each take

place one day later.

Procedures to be followed **at the CRU** or the Psychiatry Infusion Suite before, during, and after each infusion will be identical to those used during Visit 1a. Clinical ratings will continue to be obtained by the same raters who evaluated patients prior to IV infusion (CR-1) and following IV infusion (CR-2), respectively. If, at any point during treatment patients do exhibit significant psychotomimetic side effects during IV infusion, resulting in need for additional monitoring beyond 5:00 pm on the day of infusion, they will be exited from the study following additional observation at the Mt Sinai ED.

In addition to the rating instruments and scales mentioned above, rater CR1 will administer the CAPS once a week (prior to the first IV infusion, and 1 and 2 weeks after the first IV infusion, usually on Mondays unless there is a holiday or scheduling difficulties that would significantly delay the patient's participation, in which case it will be administered the following day).

At Visit 4b, approximately one week after their first infusions, participants who participate in the MRI portion of the study will undergo their second MRI scan during this visit.

At Visit 7 (2 weeks after first drug infusion), patients will again be administered the battery of cognitive tests to assess any potential changes in cognitive function compared to baseline.

Visit 7 (After all Ketamine or Midazolam infusions are completed)

Laboratory testing will be repeated three days after the conclusion of ketamine or midazolam treatment.

Patients will be assessed with the TOP-8, CAPS and the MADRS by the same rater who performed these assessments at Visit 1a prior to the first IV infusion (CR-1). Patients will also be assessed by a study physician with CGI-I and CGI-S scales, and will be asked to complete the IES-R, QIDS-SR_{16}, the POMS and the VAS.

During this visit (2 weeks after first drug infusion), patients will again be administered the battery of cognitive tests, to assess any changes in cognitive function compared to baseline.

Visits 8-11 (Weekly Follow-Ups)

Patients will be assessed with the CAPS and MADRS by the same rater who performed these assessments at Visit 1a prior to the first IV infusion, and with CGI-I and CGI-S scales by a study physician. Patients will also complete the IES-R, QIDS-SR_{16}, the POMS and the VAS.

Visits 12-16 (Monthly Follow-Ups)

Patients will be assessed with the CAPS and MADRS by the same rater who performed the assessments on the morning of Visit 1aVisit 1a (CR-1), and with CGI-I and CGI-S scales by a study physician. Patients will also complete the IES-R, QIDS-SR_{16}, the POMS, and VAS.

Visits 17-19 (Optional Open Label Phase)

Patients will be offered up to three open-label ketamine infusions. These infusions will occur over the course of up to three weeks. The same assessments indicated above will be completed on these infusion days.

Description of measures and summary table:

Both clinician-administered and validated self-report instruments are used, with the aim of measuring baseline symptomatology as well as drug actions on (1) the overall severity of the disorder, (2) the core symptoms of PTSD, and (3) depressed mood. Below is a description of the instruments used.

The Structured Clinical Interview for DSM-5 Axis I Disorders, Patient Edition (SCID-P) is a semi-structured interview that provides probe questions as well as follow-up questions to be asked by the clinician to assist in diagnosis (First et al 2002). The new version modified for DSM-5 is available from the authors (First, M.). It includes an overview to obtain information about demographics, work, chief complaint, history of present illness, past history, treatment history, and current functioning. The main body of SCID-P includes 9 modules that are designed to diagnose 51 mental illnesses in all.

The Clinician-Administered PTSD Scale (CAPS) is a structured clinical interview designed to assess the essential features of PTSD as defined by the DSM5 (Blake et al., 1995; Weathers et al., 1993, 2001). We will use the new version modified for DSM-5. The CAPS can be used to provide categorical ratings of diagnostic status as well as a quantitative index of symptom severity. Both frequency and intensity scores are derived for each individual symptom. The CAPS total score is based on an individual's response

to the 17 items that assess the frequency and intensity of current PTSD symptoms. Subscales of the CAPS will be utilized to assess specific symptom clusters. Our research group has extensive experience using the CAPS from ongoing PTSD studies.

The Treatment Outcome PTSD Scale (TOP-8) is a brief interviewer-administered scale designed specifically for the assessment of commonly occurring signs and symptoms of PTSD that are subject to change in response to treatment (Davidson et al., 1997). The TOP-8 is comprised of eight items, each measured on a scale of 0–4, with defined anchors given for each item. The items are representative of the three core features of PTSD with a maximum possible score of 32.

The Hamilton Psychiatric Rating Scale for Anxiety (HAM-A) is a widely used observational rating measure of anxiety severity. The scale consists of 14 items. Each item is rated on a scale of 0 to 4. This scale will be administered to assess the severity of anxiety and its improvement during the course of treatment. The HAM-A total score is the sum of the 14 items and the score ranges from 0 to 56. (Hamilton, 1959)

The Montgomery-Asberg Depression Rating Scale (MADRS) is a 10-item instrument used for the evaluation of depressive symptoms in adults and for the assessment of any changes to those symptoms (Montgomery and Asberg, 1979). Each of the 10 items is rated on a scale of 0 to 6, with differing descriptors for each item. These individual item scores are added together to form a total score, which can range between 0 and 60 points. The estimated time to administer this scale is 20 minutes. Inter-rater reliability of the scale is high and scores correlate significantly with those of the HAM-D. On the infusion days a modified MADRS will be used that will exclude the sleep and appetite items.

The Brief Psychiatric Rating Scale (BPRS) is used to assess acute behavioral changes during the administrations (Overall and Gorham, 1962). Four key BPRS items for the positive (+) symptoms of psychosis will be used: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content. Three items representing the negative (-) symptoms of psychosis will also be used: blunted affect, emotional withdrawal, and motor retardation.

The Young Mania Rating Scale, item 1 (YMRS-1) will be used to assess mood elevation on the infusion days (Young et al., 1978).

The Clinician-Administered Dissociative States Scale (CADSS) is used to measure

dissociative effects during the administrations (Bremner et al., 1998). The scale includes 19 questions and 8 observer ratings scored from 0 (not at all) to 4 (extremely). The CADSS measures impairment in body perception, environmental perception, time perception, memory impairment, and feelings of unreality.

The Patient Rated Inventory of Side Effects (PRISE) is a patient self-report measure used to identify and evaluate the tolerability of side effect symptom. This scale is a 7 item assessment of the side effects in the following symptom areas; gastrointestinal, heart, skin, nervous system, eyes/ears, genital/urinary, sleep, sexual functioning, and other. Each domain has multiple symptoms and for each domain the patient rates whether these symptoms are tolerable or distressing. The administration time is less than 5 minutes.

The Clinical Global Impression (CGI) scale assesses treatment response in psychiatric patients. The administration time is 2 minutes. This scale consists of three items: Severity of Illness (item 1); Global Improvement (item 2); and Efficacy Index (item 3). Item 1 is rated on a seven-point scale (1 = normal, 7 = among the most extremely ill patients) as is item 2 (1 = very much improved, 7 = very much worse). Each includes an additional response of “not assessed.” Item 3 is rated on a four-point scale (from “none” to “outweighs therapeutic effect”). Only items 1 (CGI-Severity or CGI-S) and 2 (CGI-Improvement or CGI-I) will be used.

The Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner Oquendo et al., 2007) is a comprehensive, semi-structured interview measure that uniquely measures the full spectrum of suicidality including passive and active suicidal ideation, suicidal intent as well as suicidal behaviors.
The Impact of Event Scale-Revised (IES-R) is one of the most widely used self-report measures of stress reactions to traumatic events (Weiss and Marmar, 1996). It measures both intrusion and avoidance. A 2002 review that evaluated its psychometric properties revealed high internal consistencies for both subscales (intrusion: mean $\alpha = 0.86$; avoidance: mean $\alpha = 0.82$), adequate test-retest reliability for intervals of >1 year, and good internal and external validity. Correlations between IES subscales and PTSD diagnosis assessed with the CAPS are high (>0.75). The IES is considered particularly useful as a measure of the intrusive and avoidant processes that mediate between the experience of trauma and subsequent adjustment (Sundin and Horowitz, 2002). The total score can range from 0 to 75.

The Posttraumatic Stress Disorder Checklist (PCL-5) is a 20-item self-report measure

reflecting DSM-5 symptoms of PTSD. The PCL-5 measures symptoms in response to stressful situations (Blake et al., 1995; Weathers et al., 1993, 2001).

The Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR) is a 16-item self-rated instrument designed to assess the severity of depressive symptoms present in the past seven days (Rush et al. 2003). The 16 items cover the nine symptom domains of major depression, and are rated on a scale of 0-3. Total score ranges from 0 to 27, with ranges of 0-5 (normal), 6-10 (mild), 11-15 (moderate), 16-20 (moderate to severe), and 21+ (severe).

The Childhood Trauma Questionnaire (CTQ) is a 28-item self-report instrument that assesses childhood trauma in the following areas: physical, sexual and emotional abuse and physical and emotional neglect (Bernstein and Fink, 1998). Each item is rated on a scale of 1 (never true) to 5 (very often true). The 5 subscales are then totaled, with scores ranging from 5-25 for each traumatic category.

Traumatic Life Events Questionnaire (TLEQ) The TLEQ is a 23-item self-report measure of 22 types of potentially traumatic events including natural disasters, exposure to warfare, robbery involving a weapon, physical abuse and being stalked.

Visual Analogue Scales (VAS) are used to assess subjective state changes (Bond and Lader, 1974). They are 100-mm horizontal lines marked proportionately to the perceived intensity of the subjective experience (0=not at all, to 10=extremely) for the following states: anxious, depressed, drowsy, high, hungry, and nauseous.

The Sheehan Disability Scale (SDS) is the most frequently used self-report disability measure. It has demonstrated sensitivity to impairment and changes as a result of treatment across a wide range of psychiatric disorders. The SDS asks only about current levels of impairment, providing no indication of whether the person has done better or worse in the past, thus making it a reasonable short-term outcome measure that is un-confounded by historical impressions. The dependent variable is the total score, which is based on the sum of three 10-point items (work, social life, and family life), with higher scores reflecting greater disability (Sheehan et al., 1996).

The Connor-Davidson Resilience Scale (CD-RISC) (Connor & Davidson, 2003) is a 25-item self-report scale, each rated on a 5-point scale (0-4), with higher scores reflecting greater resilience.

LOT-R (Life Orientation Test-Revised) (Scheier, M. F., Carver, C. S., & Bridges, M. W. (1994).) This 10-point self-report scale was developed to assess individual differences in generalized optimism versus pessimism.

The Medical Outcomes Study (MOS) Social Support Survey (Sherbourne & Stewart, 1991) is a 19-item self-report measure designed to assess levels of functional social support. The MOS-SS has two subscales (emotional and instrumental social support) to identify potential social support deficits.

The Purpose in Life test - Short Form (PIL-SF) (Schulenberg et al 2010) is a brief, 4-item form of the 20-item Purpose in Life test (ref). This scale asks respondents to report to what extent they have achieved their goals in life, and to what extent they perceive their life to be meaningful or purposeful.

The Posttraumatic Growth Inventory (PTGI)-Short Version (Cann et. al, 2010) is a 10-item shortened version of the PTGI self-report questionnaire (ref). It asks respondents to rate the extent to which they have changed as the result of experiencing a highly stressful life event. Items span positive changes in five domains: relating to others, new possibilities, personal strength, spiritual change, and appreciation of life.

The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (Endicott, Nee, Harrison & Blumenthal, 1993) is a self-report scale measuring the degree of enjoyment and satisfaction experienced by subjects in various areas of daily functioning. The summary scores are reliable and valid measures of these dimensions in a group of depressed subjects.

The Wechsler Abbreviated Scale of Intelligence 2-Subtest (WASI-2) is a reliable brief measure of IQ for 6 to 89 year-olds that takes 15 minutes to complete and includes Vocabulary (an estimate of verbal fluid abilities) and Matrix Reasoning (an estimate of nonverbal fluid abilities) (Donders and Axelrod, 2002). It is extensively used in clinical, educational, and research settings. Average reliability coefficient is 0.96 and test-retest reliability is 0.88.

The Profile Of Mood States –Bipolar Version (POMS - Bi) scale measures moods and feelings primarily in clinical rather than nonclinical settings. It can help to determine an individual's psychiatric status for therapy, or be used to compare mood profiles associated with various personality disorders. It is also a useful instrument in identifying the effects of drug treatments (O'Halloran et al., 2004).

The Beck Scale for Suicide Ideation (BSS) (Beck , Kovacs et al., 1979) is a 21-item self or clinician-administered instrumentation used to measure the current intensity of patients' specific attitudes, behaviors and plans to commit suicide. The BSS consists of 5 screening items. Three items assess the desire to live or to die and two items assess the desire to attempt suicide. If the subject reports any passive or active suicidal ideation the additional 14 items are administered.

The Massachusetts General Hospital (MGH) Cognitive and Physical Functioning Questionnaire (CPFQ) (Fava et al, 2009): This is a brief (7-item), validated self-report inventory to assess rates of significant cognitive symptoms such as memory, attention and executive function difficulties.

The Snaith-Hamilton Pleasure Scale (SHAPS) (Leventhal, A.M., et al., 2006) This 14-item, self-report was developed for the assessment of hedonic capacity. The inability to experience pleasure, anhedonia, is recognized as a hallmark symptom of depression.

The Perceived Stress Scale (Cohen, S et al., 1983). A 10-item self-report scale that was developed to measure the degree to which situations in one's life are appraised as stressful.

The State-Trait Anxiety Inventory (STAI) (Spielberger 1985) is a self-report instrument that differentiates between the temporary condition of state anxiety and the longstanding quality of trait anxiety. With a fifth grade reading level, the STAI is suitable for individuals who are 15 years old and older.

g) Specimen Banking

Blood samples for assessment of plasma ketamine, norketamine, midazolam, and α-hydroxy-midazolam levels will be obtained 30, 60 minutes, 90 minutes, and 120 minutes after the start of the first infusion only. Blood will be drawn from a heplock contralateral to the administration IV. Plasma ketamine and norketamine levels, and plasma midazolam and α-hydroxy-midazolam levels will be assayed using validated liquid chromatography procedures. Blood samples will be stored in a freezer at the CRU with appropriate labeling. The specimen will be stored until the end of the study or for interim analysis. They will be accessed only by study personnel. The information provided with the specimen include randomization number of the participant, visit number, type of sample and project identification information.

h) Data Management and Confidentiality

All data collected will be kept confidential and used for research purposes only. Each participant will be assigned a coded identifier that will be used to associate stored data with each participant. Questionnaires, forms, and results of medical and laboratory tests will not have identifiers that can be linked to the participant other than the coded identifier. Diagnostic interviewers will only enter coded identifiers on their notes and forms. The only forms that will contain the participants' names and identifying information will be the consent forms, which will be stored in a locked file in the principal investigator's locked office. The list associating participants' names with coded identifiers will be maintained separately from the data and in a locked file. No participant's identifying data will be published. All electronic records will be kept confidential to the extent permitted by law, stored in a file (including the linking file) on an electronically secure database in the Department of Psychiatry at MSSM maintained by Sinai's IT department. This database is password protected and only study personnel will be given the password. The results will be gathered with a coded identifier. We will keep a master log that will allow us to interpret the results by matching them with clinical data.

Data will be stored in a cabinet that is in a locked room. The cabinet is secured with a lock, and only the PI and his associates have access to that computer. Data will be stored by the participant's coded identifier only.

Access to this information will be limited to Drs. Adriana Feder, James Murrough, Andrew Perez, and Dan Iosifescu, as well as members of their research group, namely study clinicians and research coordinators.

Data Analysis Plan:

Partially unblinded sequential data analyses ("drug A/drug B") will be conducted each time 5 additional participants complete study procedures, under the supervision of Dr. Michael Parides, who will receive partially unblinded data from the research pharmacist. All other study investigators will remain fully blinded. Based on findings from this data analysis, if response to one drug is superior to response to the other drug, the randomization ratio will switch from 50%-50% to 60%-40% favoring the drug with superior effect.

The primary outcome is planned to evaluate the short-term effects of repeated intravenous infusions of ketamine compared to the active control (midazolam). A paired two-sample t-test will be used to compare mean CAPS scores in the two treatment groups at 2 weeks after the first study drug administration.

For the IES-R, one of the secondary outcome measures for this study, based on data from a recent study of a single infusion (Feder et al., 2014), a decrease of 30 (sd=10) from baseline of 45 is expected in the ketamine arm, and a decrease of 25 (sd=10) is expected in the midazolam arm. A paired t-test was chosen in order to determine whether IES-R scores improved compared to baseline and whether the change was different between treatment groups. A sample size of 40 will provide 89% power assuming a Type I error rate of 0.05.

To assess longer-term effects of repeated study drug administrations, mean CAPS scores at 7 days after the initial administration will be compared using a paired two-sample t-test. If the difference between ketamine and midazolam is statistically significant at 7 days, mean CAPS scores at baseline and at 28 days after the initial infusion will be compared between groups using a paired two-sample t-test. This sequential testing, or gatekeeping, strategy is used to preserve Type I error and increase power. In the single infusion study (Feder et al., 2014), a decrease of 27 (sd =20) in CAPS score at 7 days was seen in the ketamine arm compared to a decrease of 13 (sd = 18) in the midazolam arm. Assuming a sample size of 40, these conservative estimates would provide 96% power assuming a Type I error rate of 0.025 (using the Bonferroni adjustment to hold the family-wise error rate at 0.05).

Neuroimaging data analyses: We will preprocess imaging data using SPM8 and Neuroelf as follows (in order): realignment of functional images, co-registration of functional and structural images, normalization to MNI template, and three-dimensional smoothing with a 6 mm kernel. Inferential statistical analysis will use the general linear model (GLM) as implemented in Neuroelf. Bilateral anatomical ROIs will be created of the amygdala and insula, as well as vmPFC and dACC. Exploratory whole-brain analyses will additionally be conducted to examine group differences in contrasts of interest using paired t-tests and simple regression analyses in Neuroelf, with a threshold of $p < 0.05$, cluster-level corrected for multiple comparisons across the whole brain.

i) Provisions to Monitor the Data to Ensure the Safety of subjects

Mount Sinai	Protocol Title:	Randomized Controlled Trial of Repeated-Dose Intravenous Ketamine for PTSD
	Principal Investigator Name/Contact Info:	Adriana Feder, MD adriana.feder@mssm.edu; x89145
	Primary Contact Name/Contact Info	Sarah B. Rutter sarah.rutter@mssm.edu, x54634
	Date Revised:	January 24th, 2020
	Study Number:	HSM 14-00843, GCO 15-0265 and 14-1781

Part I: Elements of a Data and Safety Monitoring Plan

1. List the name(s) of the individual(s) at MSSM who will be responsible for data and safety monitoring of this study. For each individual, indicate their role, name, title, and department information. The Principal Investigator may be the only monitor of a study.

If the qualifications of an individual to serve as a monitor are not contained in the PPHS application, they must be added to the DSMP either as a narrative description or as a CV.

MSSM Principal Monitor:
Check One: PI:☒ Team Member: ☐ Independent:☐
Last Name: Feder
First Name: Adriana
Academic Title: Associate Professor
Department: Psychiatry
Mailing Address: 1 Gustave L. Levy Place, Box 1230
New York, NY 10029
Phone: 212-659-9145
Fax: 212-659-9291
E-mail: adriana.feder@mssm.edu

MSSM Additional Monitor:
Check One: PI: ☒ Team Member: ☐ Independent: ☐
Last Name: Murrough
First Name: James
Academic Title: Assistant Professor
Department: Psychiatry
Mailing Address: 1 Gustave L. Levy Place, Box 1230
New York, NY 10029
Phone: 212-585-4640
Fax: 212-241-3354
E-mail: james.murrough@mssm.edu

2. Justify your choice of principal monitor in terms of the assessed risk to the research subject's health and wellbeing. In high risk studies when the principal monitor is independent of the study staff, indicate the individual's credentials, relationship to the PI, and the rationale for selection.

Drs. Feder and Murrough have extensive experience in the conduct of clinical trials studying the effects of ketamine in patients with PTSD and TRD at ISMMS.

3. List the specific items that will be monitored for safety (e.g., adverse events, subject compliance with the protocol, drop outs, etc.).

Both the recruitment process and the informed consent process will be monitored by independent monitors who are not affiliated with the research team. Adverse events, subject compliance with the protocol, side effects and dropouts will also be closely monitored.

4. Indicate the frequency at which accumulated safety and data information (items listed in number 3 above and interim analysis of efficacy outcomes) will be reviewed by the monitor(s) or the Data Monitoring Committee (DMC). Although this information must be reviewed at least annually, the higher the study risks, the more frequently reviews must be scheduled.

The primary study monitors, Dr. Feder and Dr. Murrough, will monitor study progress and safety continuously. The two monitors will meet formally during a weekly lab meeting. In addition, the DSMB (see below) will review the accumulated safety and data information twice a year.

5. Where applicable, describe rules which will guide interruption or alteration of the study design.

Medical Criteria for discontinuation are as follows:

1. Changes in psychiatric symptoms at any time during the study:
   Treatment emergent mania, hypomania, worsening suicidality or psychosis
2. Emergent medical symptoms on the infusion days:
   a. During intravenous infusion day and post-administration monitoring period: in the event of tachycardia >110 beats per minute, systolic BP>160 mm Hg or diastolic BP>100mg Hg, the study physician will treat using the following preferred medications;
      i. Esmolol 100-500 mcg/kg IV titrated to reduce the heart rate and systolic BP.
      ii. Nitroglycerin 20-80 mcg IV titrated to reduce the BP to an acceptable range.

iii. Further therapy with longer acting agents such as metoprolol, esmolol and labetolol will be administered if the response to initial therapy is not adequate.

b. If three consecutive vital sign measurements (over 15 minutes) are consistently above the HR and BP limits stated above despite therapy, intravenous infusion will be discontinued.

c. If a patient becomes sedated to the point that he/she is unresponsive to verbal commands or there is complete or partial airway obstruction, intravenous infusion will be discontinued. If either of these problems occurs, the study physician will open the sealed envelope with the drug identity and treat the patient accordingly. Midazolam sedation would be reversed by using flumazenil. The patient would then be transferred to the Post Anesthesia Care Unit or an intensive care unit bed as necessary for further observation and treatment.

d. In the event that SpO_2 < 95% over 5-minute interval, the study physician will have the option of adjusting the nasal cannula position or flow rate. If the SpO_2 does not increase to 95% or greater with intervention, the study will be discontinued and further therapy will be administered by the study physician.

6. Where applicable, indicate dose selection procedures that will be used to minimize toxicity.

The dose of ketamine is fixed at 0.5mg/kg mg and that of midazolam is fixed at 0.045mg/kg, to be given over 40 min. As above, ketamine or midazolam infusion will be discontinued earlier if necessary due to side effects.

7. List any specialized grading system that will be used to evaluate adverse events (e.g., National Cancer Institute Common Toxicity Criteria).

The study physician will be present at the CRU or Psychiatry Infusion Suite throughout the infusions so that potential adverse events can be evaluated and treated promptly. The study physician will remain until at least one hour following the termination of the administration or until the patient meets Aldrete criteria (good respiration, oxygen saturation, consciousness, circulation and activity). The following clinical endpoints of hypnosis will be obtained: Ramsay Sedation Scale Score, loss of eyelash reflex, inhabitation of nasal-body movement response and/or sneezing,

nystagmus and salivation. The PI will report any serious adverse events, verbally and in writing, to the Mount Sinai IRB within 48 hours.

8. Describe procedures that will be used to assure data accuracy and completeness.

There will be one project coordinator who will coordinate the database. Two volunteer research assistants will enter and verify data. To help avoid errors in data entry, limits will be set for each scale (on Excel), only allowing the range of values possible for that specific scale to be entered in those data cells. Furthermore, the total of each scale will be calculated by Excel equations to ensure accuracy.

9. Should a temporary or permanent suspension of your study occur, in addition to the PPHS, to whom (NIH, FDA, sponsor, IRB) will you report the occurrence?

This will be reported to the funding agency (we are currently applying for funding).

Part II. Data Monitoring Committee/Data Safety Monitoring Board (DMC/DSMB)

The DSMB includes the following members:, Lawrence Price MD (Department of Psychiatry, Brown University, named by ISMMS chair of psychiatry, Dr. Wayne Goodman) and Yaakov Beilin MD (Department of Anesthesiology, ISMMS). Currently, a new chair of the DSMB committee is being selected to replace Dr. Larry Siever, the previous chair. A final determination has not been made. This is the same DSMB that currently reviews all ongoing ketamine clinical trials conducted by investigators at DAC. The board will review the project's data and safety on bi-annual basis and report their findings to the PI. DSMB reports will also be made available to the Mt. Sinai PPHS. The DSMB will ensure the safety of study participants and the integrity of the data collection in the projects. To achieve this goal, the DSMB will perform an ongoing evaluation of the safety of patients participating in the clinical trial. This includes monitoring adverse events and overall clinical outcomes in the studies. Through this process, the board will evaluate the need for study termination and/or modification of study criteria for inclusion, exclusion, or discontinuation. In addition, the DSMB will be responsible for the evaluation of the adherence to written protocols regarding the protection of human subjects and the assurance of identity protection as specified in the Data Sharing

Section. The DSMB will expeditiously review all serious adverse events and perform ongoing scheduled reviews of non-serious adverse events and study dropouts.

j) Withdrawal of Subjects

Patients will be withdrawn from the double-blind treatment period if, in the investigator's opinion, there is a safety risk to the patient or a chance that the patient may deliberately injure him- or herself or others. In the event that a subject is discontinued from the study early and/or following completion of the study, the patient will continue to receive standard psychiatric care as determined by the treating psychiatrist.

However, the Principal Investigator for the research may still use the information that was already collected if that information is necessary to complete the study. Subject's health information may still be used or shared after withdrawal in cases where the subjects develop side effects.

6) Risks to Subjects

General research procedures: Research interviews will be interrupted if individuals become distressed or object to answering questions. If in the clinician's judgment a patient has worsened to such a degree that further participation would put him or her at risk, he or she will be discontinued from the study.

At any point during the study patients will be told to immediately inform their research physician if they develop a worsening of depressive symptoms, symptoms of mania, or active suicidal plans. Patients will also be encouraged to identify someone who knows them well to contact the research physician on their behalf in case manic symptoms or suicidal thoughts develop. We have included safety measures such as discontinuation of the study drug and transition to standard clinical treatment should patients worsen to a sufficient degree. These precautions are likely to be highly effective in minimizing risks.

Infusions and post-infusion days: Patients will be closely monitored by the study physician, study psychiatrist, and nursing staff at the Infusion Suite or CRU. Assessments will be administered repeatedly during immediately and 120 minutes following intravenous infusion to ensure that symptoms, including any potential psychotomimetic

symptoms do not worsen. A physician will be on-call during off hours.

Risks of IV catheterization and minimization of this risk: The risks of venipuncture include pain, bruising, and to a lesser degree, the risk of infection at the injection site, dizziness or syncope during or after the blood draw. To limit risk, these procedures will be performed by staff members who are experienced in venipuncture, using sterile technique.

Risks associated with clinical interview and scale administration, and minimization of these risks: During the clinical interviews, patients may express fatigue, frustration, or anxiety in response to the questions. In these situations, the interview will be stopped and depending on the situation, the patient may then 1) take a rest period and resume later, 2) be rescheduled for a later appointment, or 3) decide to terminate the exam. There always exists the potential for loss of private information; however, there are procedures in place to minimize this risk.

Pertaining to participants who complete the MRI portion of the study, the fMRI procedure is very safe and exposes the study subjects to minimal risk or discomfort. The MRI scanning involves the subject placing their head in a tube and some subjects may experience a feeling of claustrophobia while in the scanner. However, a study investigator will be present for all scanning sessions in case of any unexpected complications. In addition, the participant will remain in verbal contact with a study investigator (via intercom) throughout the procedure so that they may communicate immediately any problems, or express a desire to terminate the scan at any time.

Follow-ups: Patients will be closely monitored by a physician at regular appointments 3 times per week for the first 2 weeks, i.e., during the period of intravenous infusions and one more visit after infusions are completed. Post-study, patients will be followed weekly for one month or until relapse, defined by CAPS administration, and thereafter monthly for up to 6 months from randomization or until relapse (defined by CAPS administration). In addition, a psychiatrist knowledgeable of the study will be on-call during off hours. Patients will be informed that if their clinical condition deteriorates during the study, they may be hospitalized. Individuals may be hospitalized if they exhibit worsening of their symptoms, including becoming suicidal. In this case or if participants discontinue treatment they will receive standard short-term clinical treatment as long as they remain on a voluntary basis. However, if they do not remain on a voluntary basis, then they may be transferred to a local hospital for further treatment. If individuals are hospitalized elsewhere, ISMMS will not cover the costs associated with that hospitalization.

Patients will be told to immediately inform their research physician if they develop suicidal ideation or symptoms of mania, or a worsening of depressive, anxiety or PTSD symptoms. They will also be encouraged to identify someone who knows them well to contact the research physician on their behalf in the event suicidal thoughts or manic symptoms develop. As an additional safeguard, we will utilize in this study a treatment contract, and will only include patients who are able to identify a family member/physician/friend who agrees to participate in this contract. We have successfully used similar treatment contracts in other studies at DAC.

Acute Ketamine Side Effects: Ketamine is a general anesthetic for human and veterinary use with a good safety profile. Over the past several decades, ketamine has been administered as an anesthetic to millions of adults and children. In addition, it has been used for years in psychophysiological studies in normal volunteers and patients with severe mental disorders, including several studies conducted by our research group (with doses similar to those in this study). Although ketamine's anesthetic effects include respiratory changes, we will use sub-anesthetic doses of ketamine with which these changes can be prevented or minimized. We have not observed any clinically significant respiratory changes in our previous ketamine administration studies.

The reported incidence of perceptual disturbances varies from less than 5% to 69%). Perceptual disturbances can manifest as vivid dreaming, visualization of psychedelic color, suspension in space, kaleidoscopic floating, and out-of-body experiences. Some patients report the psychic experiences as bizarre or frightening, while others describe them as pleasurable, joyful, or fascinating. When such reactions occur, they are usually mild and short-limited. Studies by our research group and others suggest that the effects of ketamine administration on these symptoms are usually short-lasting (less than 60 minutes) and rarely last longer than 2 hours. The perceptual disturbances appear more commonly in those with preexisting psychosis (schizophrenia), which is why those patients with a history of psychosis are excluded.

Patients will be closely monitored by the study physician, study psychiatrist, and the nursing staff at the CRU or Infusion Suite. Assessments will be administered immediately and 120 minutes following infusion to ensure that symptoms, including any potential psychotomimetic symptoms do not worsen. A physician will be on-call during off hours.

Acute Midazolam Side Effects: Side effects associated with midazolam, especially at the sub-anesthetic dose given, are expected to be mild. Midazolam has good cardiovascular

stability, and induces only a transient and mild respiratory depression in comparison with other benzodiazepines. Midazolam produces a short-duration anterograde amnesia that is not likely to last beyond 30-60 minutes following the infusion.

7) Provisions for Research Related Injury

Medical and psychiatric resources will be available during and acutely following drug administration and subjects will be actively monitored during this period. In general, if subjects are injured or made sick from taking part in this research study, medical care will be provided. Generally this medical care will be billed to the health care insurance. However, Mount Sinai may be responsible for the costs of any research-related injury. Mount Sinai agrees to pay for those subjects without health insurance and financially vulnerable in case an emergency or injury related to the research occurs.

Patients will be told to immediately inform their research physician if they develop suicidal ideation, or a worsening of anxiety, depressive or PTSD symptoms. They will also be encouraged to identify someone who knows them well to contact the research physician on their behalf in the event suicidal thoughts.

Patients will also be provided with contact information for the study psychiatrist.

8) Potential Benefits to Subjects

The risks of this study are reasonable in relation to the anticipated benefits to the patient and his/ her environment (remission or improvement of PTSD symptoms). No other direct benefits result from study participation. All participants will receive, without cost, an extensive psychiatric and medical evaluation. All participants will receive reimbursement of travel expenses and some compensation for their time and participation.

9) Provisions to Protect the Privacy Interests of Subjects

Research coordinators will call participants from previous research studies to see if they are interested in participating in this research study. Only those participants who consented to be contacted will be reached out to. Those conducting phone screens will introduce themselves, the clinic and talk briefly about the study. The questions go from

more general questions to more specific. Only if the participant is comfortable will he/she answer more specific questions about his/her history and symptoms.

Participants are also told that answering all questions is voluntary and if anything were to make him/her feel uncomfortable they would not have to answer the questions. If a participant has any special need (e.g., only seeing a female study doctor, etc) arrangements will be made for the individual as much as possible. After assessments and interviews, participants are given the opportunity to express any concerns about how they feel post-follow-up, etc. All study assessments will be conducted in a private room. Patients will assured that all information shared with study personnel is confidential and protected by MSH policy and HIPPA.

10) Economic Impact on Subjects

No costs shall be incurred by participants for their participation in the study. In the event of an injury resulting from the research study, the facilities of Mount Sinai Hospital and professional attention will be made available to patients.

11) Payment to Subjects

Procedure	**Reimbursement**
Screening visit 1 (interview)	$50
Screening visit 2 (medical clearance)	$25
First administration day	$75
24-hour follow up	$50
Second administration day	$50
Third administration day	$50
Fourth administration day	$75
Fifth administration day	$50
Sixth administration day	$50
Study Exit Visit	$75
First Follow up	$25
Second Follow up	$25
Third Follow up	$25
Fourth Follow up	$25

Fifth Follow up	$25
Sixth Follow up	$25
Seventh Follow up	$25
Eighth Follow up	$25
Ninth Follow up	$25
MRI Scanning (x 2)	$100 per scan
Total for participation in all parts of the study, if all eight follow-up visits are needed	**$975**

Reimbursements will be made by check and will be requested on each visit day. Checks are requested through the Mount Sinai finance department and typically take 2-3 weeks to process; patients have the option of having their checks mailed directly to them or to pick them up in the office. Payment is not contingent on completing the study.

12) Consent Process

Informed consent will be obtained prior to screening in DAC, located on ISMMS premises, in a closed office with only members of the research group present. These offices are located at DAC on the 2nd floor of 1399 Park Avenue. No reference to the potential participant's identity will be made outside of closed quarters. The study team is following "SOP HRP-090 Informed Consent Process for Research." Prior to obtaining consent, a brief study synopsis will be presented and the following options will be presented to the patient by a member of the study personnel: 1) the option to hear detailed information about the study at that time, 2) the option to take a copy of the consent form home with them and to contact study personnel if they are interested, and 3) the option to decline participation or hearing more about the study. We will clearly state that participation in the research study is completely voluntary and only one of several options to consider. We will also tell the patient that his/her decision about whether or not to participate does not impact clinical care or their relationship with treatment providers. This consent process should allow adequate time for subjects to make an educated and autonomous decision. In compliance with ICH Good Clinical Practice guidelines, the consent process will be documented.

After the protocol is described to the participant and the participant's questions are answered, the participant will be asked to summarize the procedures that he/she will undergo and to describe two risks involved in the study. A capacity assessment will also be conducted by an independent psychiatrist to determine whether the participant has understood and informed consent can be provided. Only individuals who are assessed

to have the capacity to consent will participate in this study. Additionally, this study will only enroll English speaking participants. This study will not enroll non-English speaking subjects due to a lack of available validated instruments in other languages and a lack of bilingual study staff and clinicians to communicate with participants and administer clinical research interviews or rating scales.

13) Process to Document Consent in Writing

Individuals will be required to sign an informed consent form if they are interested in participating in this research study. An investigator or research coordinator listed under assurances will also sign the consent form. A copy will be given to the research participant and the original will be stored in their patient file in a locked cabinet in a locked room.

Additionally, a capacity assessment will also be conducted by an independent psychiatrist to determine whether the participant has understood and informed consent can be provided. Only individuals who are assessed to have the capacity to consent will participate in the study. An independent capacity assessment form will be signed by this psychiatrist if he/she grants capacity to the patient to participate in this study.

14) Vulnerable Populations

Include	*Exclude*	*Vulnerable Population Type*
	x	*Adults unable to consent*
	x	*Individuals who are not yet adults (e.g. infants, children, teenagers)*
	x	*Wards of the State (e.g. foster children)*
	x	*Pregnant women*
	x	*Prisoners*

Individuals who are economically or educationally disadvantaged persons. In the Mount Sinai catchment area we expect to enroll individuals who are economically or educationally disadvantaged. Additional efforts will ensure that these persons understand all of the proposed research. These efforts would include: (1) not preferentially enrolling vulnerable patients; (2) providing a consent document and all other information to subjects in terms they can fully understand; (3) not exerting any

overt of covert coercion; (4) offering payment amounts that are not considered to be coercive.

15) Control of Drugs or Devices

Ketamine and midazolam will both be stored at the ISMMS pharmacy.

16) Multi-Site Human Research (Coordinating Center)

N/A

17) Community-Based Participatory Research

N/A

18) Sharing of Results with Subjects

Subjects can be provided with a copy of their medical work up (labs, ECG, etc) upon written request to the PI. After analysis of data, outcomes and results may be shared with participants upon request.

19) IRB Review History

N/A

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