Adding Trauma-focused Psychotherapy To Ketamine Treatment For Chronic PTSD: A Pilot Study
NCT04889664
Principal Investigator: Adriana Feder, MD
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Principal Investigator: Adriana Feder, MD

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
1.1, 1.2, 1.3, 3, 4.1, 4.4, 5.5, 6.1.2, 6.3, 8.1, 8.2, 8.3.5, 9.1, 9.3, 9.4.3	**All eligible participants will receive six (6) infusions of ketamine and five (5) WET sessions, regardless of responder status, and will be assessed weekly for 12 weeks following the start of WET. After 12 weeks, participants who demonstrate ≥ 30% improvement at the 12-week assessment will be assessed monthly for up to 24 weeks following the start of WET or until loss of response.**	Based on our recent meeting with a panel of experts in the field, and following their recommendation, we would like to offer all 6 infusions and 5 WET sessions in order to capture more gradual effects of WET and the potential effects of Ketamine + WET in both responders and non-responders to ketamine. The primary aim of the study remains unchanged.
1.3, 8.1, 11	**Adding Hood Mysticism Scale and Psychological Insight Questionnaires to Infusions 1 and 2.**	We would like to add these self-report scales to the first two infusions to assess participant experiences during the ketamine infusions.

Table of Contents

Effective Date: 8/23/2023
End Date:4/3/2024

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Adding Trauma-focused Psychotherapy to Ketamine Treatment for Chronic PTSD: A Pilot Study

Study Description: Current treatments for posttraumatic stress disorder (PTSD) do not work for a significant proportion of individuals with PTSD, or work only partially, leaving persistent and disabling residual symptoms. Our research team has led the development of ketamine for the treatment of chronic PTSD. After our initial, proof-of-concept randomized controlled trial (RCT) of a single ketamine infusion in individuals with chronic PTSD showed promising results, we completed the first RCT of repeated intravenous ketamine infusions where individuals with chronic PTSD received a course of six ketamine infusions (vs. active placebo midazolam infusions) and demonstrated a rapid and robust improvement in PTSD symptoms. The median time to loss of response, however, was 27.5 days following the course of infusions, making it imperative to investigate novel approaches aimed at preventing symptom relapse following ketamine treatment. We thus propose a proof-of-concept, open-label pilot study to evaluate the efficacy of adding an evidence-based, brief and scalable trauma-focused psychotherapy, Written Exposure Therapy (WET), to a course of ketamine infusions in maintaining PTSD symptom improvement over time, in

participants with chronic PTSD.. To accomplish this aim, we will enroll individuals who meet DSM-5 criteria for chronic PTSD.

Eligible patients will receive a total of 6 ketamine infusions and 5 WET sessions. The primary outcome will be change in PTSD symptom severity assessed by the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) from baseline (before the first infusion) to 12 weeks from the start of WET. All participants will be assessed until week 12 following the start of WET. They will complete weekly assessments from baseline until 6 weeks from the start of WET, as well as assessments at 12 weeks from the start of WET. At other time points between 6 and 12 weeks, participants will be assessed weekly, or less frequently as tolerated.
Although initial response to ketamine (PTSD and co-morbid depressive symptom improvement) will be assessed after the first four infusions (prior to starting WET), all participants will receive 6 infusions and 5 WET sessions regardless of their initial response to ketamine.
Participants will be asked not to make any changes to any concomitant treatment (i.e., medication dosages, psychotherapy) during this period.

Thereafter, participants who remain improved at the 12-week time point (compared to baseline) will then receive additional monthly assessments up to 24 weeks or until loss of this improvement.

We will also evaluate whether extinction learning ability –assessed with a computerized extinction learning task– is associated with PTSD symptom improvement from baseline to 12 weeks from the start of WET. If demonstrated to result in significant and maintained PTSD symptom improvement, this novel combined treatment may represent a promising intervention for individuals with chronic PTSD, deserving further study.

Objectives:

Primary Objective: To evaluate the efficacy of adding WET to ketamine therapy in improving PTSD symptoms from baseline to 12 weeks from the start of WET, in individuals with chronic PTSD .

Secondary Objectives (exploratory): (1) To evaluate improvement in PTSD symptoms from baseline to 6 weeks, and on other measures from baseline to 6 weeks, and from baseline to 12 weeks; (2) To evaluate durability of PTSD symptom improvement beyond 12 weeks in patients who remain improved, up to 24 weeks; (3) To evaluate whether ketamine-induced change in extinction learning is associated with improvement in PTSD symptoms from baseline to 12 weeks from the start of WET.

Endpoints:

Primary Endpoint: Change in PTSD symptom severity assessed by the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) from baseline to 12 weeks from the start of WET.

Secondary (Exploratory) Endpoints:

	- Change in PTSD symptom severity from baseline to 6 weeks from the start of WET, assessed by the CAPS-5. - Change on other measures, including the Montgomery-Asberg Depression Rating Scale (MADRS), Sheehan Disability Scale (SDS), and Clinical Global Impression severity and improvement (CGI-S and CGI-I), from baseline to 6 weeks, and from baseline to 12 weeks. - In participants with maintained PTSD symptom improvement after 12 weeks, change on the CAPS-5 and other measures, from baseline to 16, 20, and 24 weeks. - Additionally, change from baseline to 24 hours after the first ketamine infusion, at each ketamine infusion day, and 24 hours after the 4th infusion, on the Impact of Events Scale (IES-R) and Quick Inventory of Depressive Symptomatology – Self-Report (QIDS-SR), both with past-24-hour recall.
Study Population:	Up to N=15 participants with chronic PTSD will be enrolled in the study. Participants will be aged 18-70 years, male or female, with a current primary diagnosis of chronic PTSD according to DSM-5 and at least moderate current illness severity, as determined by a score of 30 or greater on the CAPS-5. Participants will be recruited from the greater New York City area.
Phase:	2
Description of Sites/Facilities Enrolling Participants:	This will be a single-site study, carried out at the Icahn School of Medicine at Mount Sinai (ISMMS) in New York City, United States.
Description of Study Intervention:	**Ketamine:** Participants will receive six (6) intravenous ketamine infusions. All ketamine infusions will be administered by a study physician credentialed for ketamine administration at Mount Sinai, at subanesthetic doses of 0.5 mg/kg over 40 minutes at each administration, and a frequency of three times per week over two consecutive weeks. Participants will also receive 5 WET sessions (the first 2 WET sessions will be interleaved with the last 2 infusions, each on a different day). After four (4) ketamine infusions, participants will begin WET sessions. All participants will receive two additional ketamine infusions, interleaved with 5 WET sessions. **Written Exposure Therapy (WET):** WET consists of 5 sessions, with the first session lasting 1 hour and each subsequent session lasting approximately 40 minutes. The first session includes psychoeducation about common trauma reactions and the treatment rationale, presented

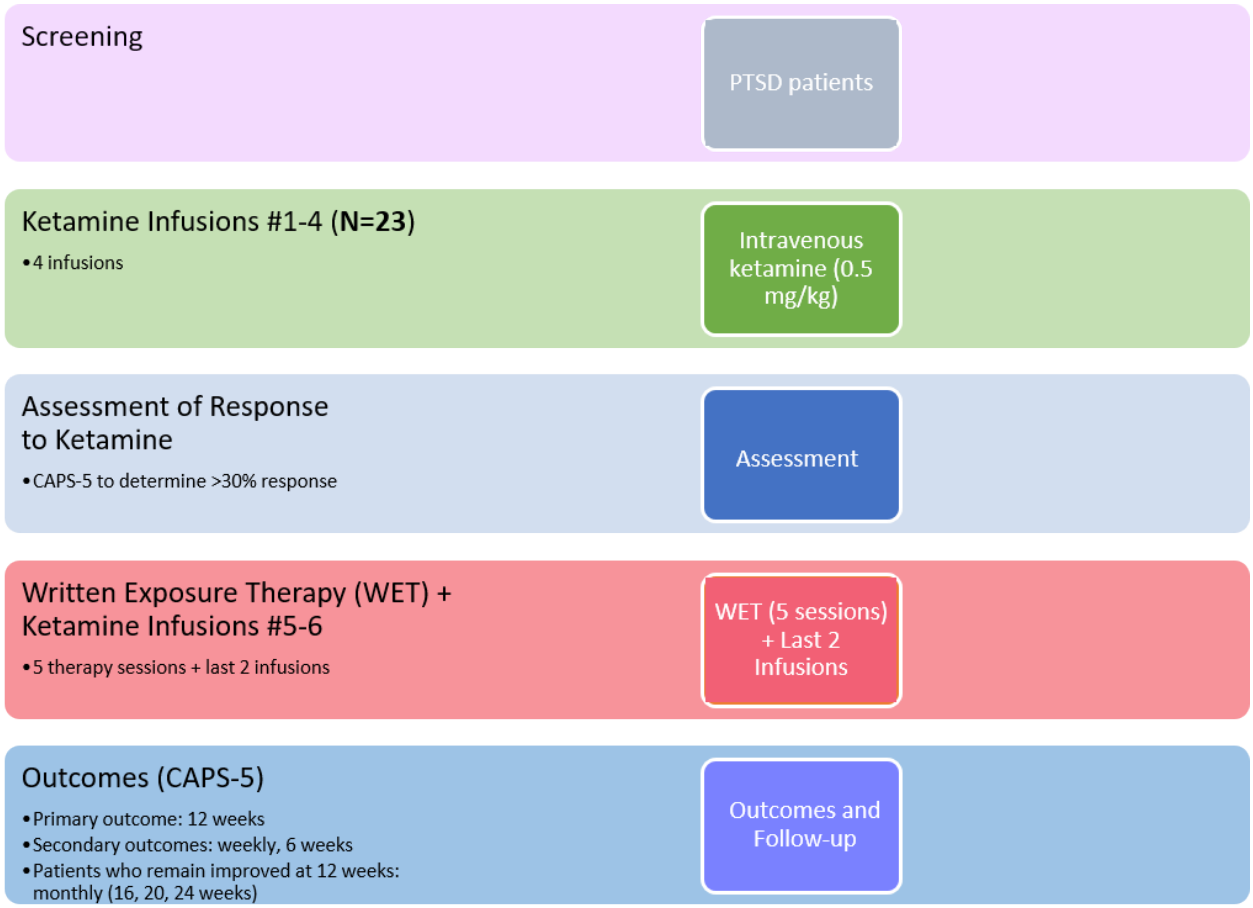
by the therapist. The participant is then given general instructions for completing the trauma narratives and specific instructions for completing the first 30-minute narrative during that first session. All WET sessions begin with the therapist reading the specific writing instructions, clarifying any questions the participant might have, and leaving the instructions with the participant for the 30-minute writing session. Writing instructions begin with a focus on the details of the trauma and then shift to the meaning of the trauma event. After 30 minutes of writing, the therapist stops the writing and conducts a 5-10 minute check-in regarding how the writing session went for the participant.

Study Duration: The study is anticipated to take place over 48 months.

Participant Duration: Participants will be in the study for up to 27 weeks. See schema in section 1.2 below for a summary.

1.2 SCHEMA

Figure 1. ***Flow diagram***



1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening	Baseline	Ketamine Infusions	24 hour Follow-Up Visit	Assessment of Response to Ketamine	WET Sessions	Weekly Assessment Until 12 weeks	Monthly Assessment Until Loss-of-Response
	Day -28 to 0	Visit 1a, Day 1	Visit 1a-9; Days 1, 3, 5, 8, 11, 12	Visit 1b, Day 2	Visit 5, Day 9	Visit 6-12, Days 10, 12, 16, 18, 22	Visits 10, 13-23, Days 12, 19, 26…	Visits23-26, Days 33…
Informed consent	x							
Demographics	x							
Medical history	x							
SCID-5	x							
CAPS-5	x	x			x		x	x
MADRS	x	x			x		x	x
WTAR	x							
MoCA	x							
IES-R		x	x	x	x			
QIDS-SR		x	x	x	x			
PCL-5	x	x			x		x	x
MOS-5		x					x[1]	
CES		x					x[1]	
PACT		x					x[1]	
CTQ	x							
TLEQ	x							
SDS	x	x		x	x		x	x
HMS			x[2]					
PIQ			x[2]					
C-SSRS	x	x			x		x	x
CADSS		x	x					
BPRS		x	x					
YMRS		x	x					
Extinction Learning Task	x				x			
CGI	x	x	x	x	x		x	x
Concomitant medication review	x	x	x	x	x		x	x
PRISE	x	x	x	x	x		x	x

Adverse event review and evaluation	x	x	x	x	x	x	x	x
Physical exam (including height and weight)	x							
Vital signs	x		x					
Weight	x		x					
EKG	x							
Routine labs	x							
Plasma ketamine and norketamine levels			x[3]					
Urine pregnancy test	x		x					
Urine drug screen (UTOX)	x		x					
Ketamine infusion (0.5 mg/kg)			x					
Written Exposure Therapy (WET)						x		
Complete Case Report Forms (CRFs)	x	x	x	x	x	x	x	x

[1] *Visit 14 and 23 only*
[2] *only at Infusions 1 and 2*
[3] *only at Infusion 1*

2 INTRODUCTION

2.1 STUDY RATIONALE

Posttraumatic stress disorder (PTSD) is a chronic and disabling condition. Trauma-focused psychotherapies for PTSD have the strongest evidence base. Access to these specialized forms of therapy, however, is often limited by geographic, economic, and time-commitment barriers, as well as need for extensive therapist training. Additionally, 25-40% of patients drop out of treatment prematurely. There is thus a strong need to develop more efficacious and scalable treatments for PTSD.

Recent evidence from our research group showed efficacy of repeated intravenous (IV) infusions of ketamine at sub-anesthetic doses (0.5 mg/kg) in rapidly improving PTSD symptoms in patients with chronic PTSD, as well as co-morbid depressive symptoms. However, these effects are time-limited, with loss of initial response to ketamine within 2 to 4 weeks following a course of six infusions. Additionally, results from pre-clinical studies suggest that ketamine administration might facilitate fear extinction learning.

Building on these findings, the current project will evaluate the efficacy of **adding Written Exposure Therapy (WET) to a course of repeated IV ketamine infusions** in improving PTSD symptoms from pre-

infusion baseline to 12 weeks from the start of WET, in patients with chronic PTSD. WET is a brief, 5-session evidence-based written trauma-focused therapy without in between-session assignments, with demonstrated efficacy and low dropout rates in patients with PTSD. WET will be administered to participants starting after they receive four initial ketamine infusions; the first WET sessions will be interleaved with two additional ketamine infusions to take advantage of a window of increased neuroplasticity potentially induced by repeated ketamine infusions. WET be administered on different days as the ketamine infusions.

2.2 BACKGROUND

1. SIGNIFICANCE

Chronic posttraumatic stress disorder (PTSD) is a prevalent and disabling disorder.[1,2] There is an urgent need for the development of novel treatment interventions for this disabling condition, as currently available treatments have limited efficacy.[3-5] Our research group has led the development of ketamine administration for the treatment of chronic PTSD, demonstrating a rapid and robust improvement in PTSD symptoms following a course of six infusions.[6-8] Additionally, recent years have seen a rapidly growing interest in the potential synergistic effect of ketamine infusions and psychotherapy,[9,10] but only open-label pilot studies have been published to date, including only one in individuals with PTSD (n=10).[11-13] Our proposed open-label trial is the first of which we are aware to evaluate the efficacy of adding a trauma-focused psychotherapy, Written Exposure Therapy (WET), to a course of ketamine infusions in maintaining ketamine response over time in individuals with chronic PTSD who demonstrate a rapid and clinically significant response to initial ketamine infusions. If demonstrated to be efficacious, this novel combined treatment may represent a promising intervention worthy of additional study for the broader population of individuals with chronic PTSD.

1.A. Chronic PTSD and insufficient efficacy of currently available treatments. Only two medications [selective serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine] are FDA-approved for the treatment of PTSD, with two additional medications showing moderate-level efficacy. Only about one third of individuals with PTSD achieve remission with SSRIs, with another third showing symptom improvement; thus, about two thirds of patients are either treatment non-responders or partial responders.[3,5,14] Although trauma-focused psychotherapies have the most evidence base for the treatment of PTSD, they require extensive therapist training and significant time commitment on the part of patients; these therapies are associated with significant rates of non-response and treatment dropout.[15,16]

1.B. Ketamine as an emerging treatment for PTSD. In recent years, clinical trials conducted by our research team have led the development of ketamine as a novel treatment for chronic PTSD. Ketamine, a noncompetitive glutamate N-methyl-D-aspartate (NMDA) receptor antagonist, was first FDA-approved as an anesthetic and analgesic agent several decades ago.[7] Following initial evidence of its efficacy for treatment-resistant depression (TRD),[17] we conducted the first proof-of-concept RCT of a single IV infusion of ketamine in individuals with chronic PTSD (compared to the psychoactive placebo midazolam), showing rapid and significantly greater improvement following ketamine administration.[6] Ketamine was well-tolerated in patients with PTSD, with only transient emergence of dissociative symptoms during infusion. Continuing our research on ketamine for the treatment of PTSD, we then completed the first RCT of repeated IV ketamine infusions for chronic PTSD, compared to repeated midazolam infusions, demonstrating significantly greater efficacy of ketamine (67% treatment responders in the ketamine

group, compared to 20% responders in the midazolam group) following a course of six infusions administered over two consecutive weeks.[8] This rapid and robust improvement in PTSD symptoms lasted for several weeks, with median time to relapse occurring 27.5 days after the full course of infusions, making it imperative as the next step to investigate novel approaches aimed at preventing symptom relapse following this very promising treatment for PTSD.

1.C. Neurobiology of PTSD and Ketamine Mechanisms of Action.

1.C.1. Chronic stress, PTSD, disrupted synaptic connectivity and abnormal glutamatergic transmission. Glutamate, the principal excitatory neurotransmitter in the brain, is crucial to learning and memory formation via strengthening of synaptic connections, including the formation of trauma memories.[18,19] Pre-clinical studies have demonstrated that chronic stress is associated with atrophy of dendrites and synaptic loss in the hippocampus and medial prefrontal cortex (mPFC), resulting in dysfunction of glutamatergic transmission.[20,21] It has been proposed that recurrent intrusions of trauma memories experienced by individuals with chronic PTSD represent a form of chronic stress, in turn associated with maintenance and worsening of disrupted synaptic connectivity and abnormalities in glutamatergic transmission, increasingly understood as key biological abnormalities underlying the pathophysiology of PTSD.[22,23]

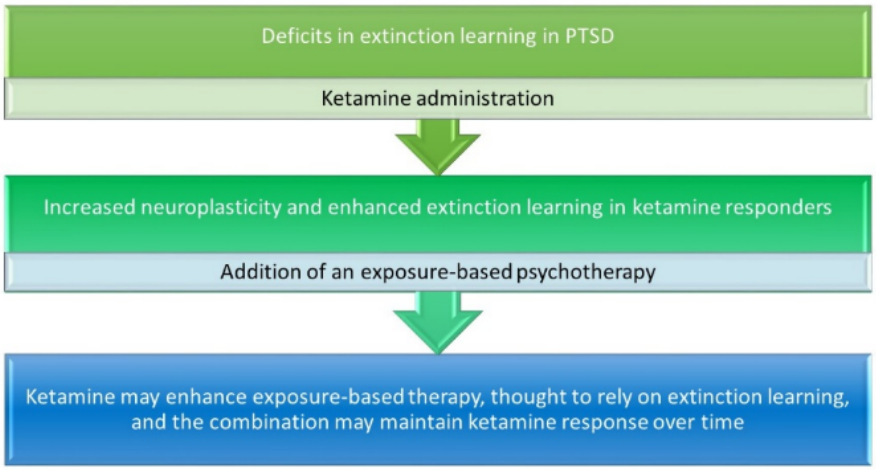
1.C.2. Fear extinction abnormalities in chronic PTSD. Alterations in fear processing and regulation characterize PTSD and are thought to contribute to the persistence of PTSD symptoms.[24] Key among these alterations is impaired fear extinction learning, assessed by repeatedly presenting a conditioned stimulus without the unconditioned stimulus.[24] Extinction learning involves learning that certain stimuli previously associated with danger or a trauma (e.g., a quiet street) are now safe (e.g., do not signify that an assault is imminent). Successful fear extinction involves formation of a new memory of safety, which overlays the original fear memory and relies on intact ventromedial prefrontal cortex (vmPFC) function.[25] Several studies have found fear extinction deficits in individuals with PTSD, in the form of persistent abnormal fear during extinction learning or reduced extinction recall upon testing during a subsequent session.[26-29] Deficits in fear extinction have been proposed to underlie a range of PTSD symptoms, including intrusions and heightened arousal.

1.C.3. Mechanisms underlying the effects of ketamine: Reversal of disrupted synaptic atrophy, enhancement of fear extinction learning. Studies in animal models have yielded insights into the mechanisms of action of ketamine. In rats first subjected to chronic unpredictable stress for 21 days, a single dose of ketamine was shown to reverse, within 24 hours, stress-induced behavioral deficits, synaptic atrophy, and pyramidal neuron dysfunction in the prefrontal cortex (PFC).[30] In individuals with chronic PTSD, ketamine is thought to work by rapidly restoring disrupted synaptic connectivity.[22,23] While neuroimaging studies examining the effects of ketamine in PTSD have not yet been published, ketamine was shown to *normalize disrupted functional dysconnectivity* between PFC/subcortical regions and the rest of the brain in patients with major depressive disorder, 24 hours post-administration.[31] Additionally, results from animal studies employing fear-conditioning paradigms suggest that *ketamine enhances fear extinction learning*. In one study of fear-conditioned rats, ketamine administration enhanced the effects of fear extinction training, resulting in reduced return of fear a week later upon exposure to the original fear conditioning context, mediated by mTORC1 signaling in the mPFC.[32] In a mouse model of PTSD, repeated ketamine administration also enhanced the effects of fear extinction training, resulting in reduced relapse of fear associated with increased brain-derived neurotrophic factor (BDNF) in the hippocampus and mPFC.[33] Findings to date suggest that ketamine might open a window of increased

neuroplasticity and enhanced fear extinction learning, during which the efficacy of psychotherapeutic interventions might be enhanced.[7,9,10,22]

1.D. Adding Psychotherapy to Ketamine Treatment for PTSD: Potential for Synergistic Effect: As the effects of ketamine administration in individuals with PTSD (or TRD) are rapid and robust, a key next step in treatment research is to identify strategies to maintain this initial response to ketamine over time. In this context, interest in leveraging a ketamine-induced temporary window of increased neuroplasticity and enhanced learning by adding psychotherapy to ketamine treatment has grown significantly in recent years.[7,9,10,22]

Figure 2: Potential Synergistic Effect of Adding an Exposure-based Therapy to Ketamine Treatment for PTSD



Open-label pilot studies adding psychotherapy to ketamine treatment have been conducted in patients with TRD (cognitive-behavioral therapy, CBT) and with obsessive-compulsive disorder (exposure-based CBT),[11,12] and most recently in PTSD (prolonged exposure, PE).[13] *Exposure-based psychotherapies* have the most empirical support for the treatment of PTSD.[14] A key mechanism thought to underlie these therapies, including WET, is *fear extinction learning.*[34-37] Following repeated exposure to traumatic memories in a therapeutic context, individuals gradually learn the safety of previously conditioned PTSD symptom triggers.[36,37] As pre-clinical research suggests that *ketamine enhances fear extinction learning*, the addition of an exposure-based therapy to ketamine treatment might have a synergistic effect, helping maintain response to ketamine over time (see **Figure 2**). An open-label pilot study combining ketamine infusions (three infusions, administered weekly) with a course of PE therapy in a small sample (n=10) of veterans with chronic PTSD was recently published.[13] While results suggest the feasibility of adding an exposure-based psychotherapy to ketamine treatment, the potential efficacy of this approach in maintaining response to ketamine over time needs to be formally studied. Of note, in this pilot study, which employed a 10-session traditional Prolonged Exposure (PE), 50% of participants dropped out prior to completing therapy.[13] In our proposed trial, we anticipate that the selection of WET, a brief and highly tolerable exposure-based therapy, will be associated with much lower participant dropout.

1.E. Written Exposure Therapy (WET) is an evidence-based, brief and scalable exposure-based psychotherapy for the treatment of PTSD, co-developed by Co-Investigator Dr. Denise Sloan, and designed to be a tolerable and efficient exposure-based treatment for PTSD that does not include between-session assignments. WET evolved from a careful and systematic series of studies to identify necessary components for successful PTSD treatment.[38] The minimal therapist-patient contact, nominal time needed to train therapists, and brevity of treatment results in an approach that addresses many of the

challenges identified with implementing other exposure-based psychotherapies for PTSD.[38,39] Fundamental components of WET include a treatment rationale, psychoeducation, and directing individuals to write repeatedly about the details of a traumatic stressor linked to their symptoms, with particular attention to felt emotions and the meaning of the traumatic event.[38] Clinical trials conducted by Sloan and colleagues have demonstrated the efficacy of WET in reducing PTSD symptom severity, including in a non-inferiority RCT comparing WET to cognitive processing therapy (CPT),[40,41] one of the therapies with highest evidence base for the treatment of PTSD.[42] WET is also highly tolerable and associated with very low patient attrition,[40,41] and is included among the recommended PTSD treatments in the VA/DoD Clinical Practice Guidelines for managing PTSD.[14]

1.F. Extinction learning as a potential predictor of PTSD symptom change following repeated ketamine + WET. The collective findings summarized above (and in **Figure 2**) constitute the scientific rationale for evaluating ketamine-induced improvement in extinction learning as a predictor of response to ketamine + WET (Aim 2). While better extinction learning prior to starting exposure therapy has been hypothesized to predict better outcomes, this has rarely been studied, with the exception of two neuroimaging studies evaluating extinction learning as a predictor of response to exposure therapy in individuals with public speaking anxiety and spider phobia, respectively. Better extinction learning pre-intervention, and neural activation during extinction learning, predicted higher post-intervention symptom reduction, assessed in the first study two weeks post-intervention.[43,44] The authors of the second study conclude that "boosting the extinction circuitry may be a target for improving exposure therapy success."[44] We are not aware, however, of any published study examining extinction learning as a predictor of response to exposure-based psychotherapy for PTSD.

Some studies of exposure-based psychotherapies have investigated whether fear activation, necessary for fear extinction to occur, predicts response to psychotherapy. Of particular relevance to the proposed study, cardiovascular activation during the first WET session was found to predict PTSD symptom improvement, suggesting that fear extinction learning is a mechanism underlying WET.[34,35] In other studies of exposure-based therapies for PTSD, higher fear activation to trauma reminders prior to starting therapy or during the first session –measured by coding participants' facial fear expression, acoustic startle, skin conductance, or heart rate reactivity– predicted great PTSD symptom reduction in response to therapy.[45-47] In particular, higher fear activation was found to predict better response to exposure-based treatment specifically in participants receiving D-cycloserine (DCS) as a potential exposure therapy-enhancing agent.[46] In our proposed study (Aim 2), we will evaluate whether ketamine-induced change in extinction learning, assessed with an online Extinction Learning Task[48] sensitive to PTSD (see **Preliminary Data**), predicts response to ketamine + WET in individuals with chronic PTSD.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Risks to privacy and confidentiality:

As the research study involves collection of protected and sensitive health information, there is a potential risk of loss of confidentiality. This risk will be conveyed to subjects as part of informed consent and will be minimized by using Standard Operating Procedures at our Depression and Anxiety Center, which comply with Health Insurance Portability and Accountability Act rules.

Risks associated with blood draw or insertion of intravenous canula:

Subjects might feel pain during blood draw or when IV is inserted, and can develop bruising, and rarely, infection. The sight of blood or insertion of IV canula may also cause dizziness or brief loss of consciousness due to vasovagal response. Therefore, all blood draws will be conducted by trained personnel, using aseptic precautions, and in a setting where the subject is resting comfortably and the risk of fall is minimized.

Risks associated with psychological questionnaires and assessments:

Answering questions related to mental health and past experiences may be stressful. Research interviews will be interrupted if subjects become distressed or object to answering questions. If in the judgment of the PI or study-affiliated psychiatrist, the patient has worsened to such a degree that further participation would put the patient at risk, then the subject will be discontinued from the study and provided appropriate clinical care.

Risks associated with ketamine infusion:

Ketamine is an analgesic agent and general anesthetic for human and veterinary use. It also has dissociative and psychedelic properties. For that reason, ketamine was categorized as a Schedule III drug in the Controlled Substance Act in August 1999. Over the past several decades, ketamine has been administered as an anesthetic to several million adults and children and has a very favorable safety profile. In addition, it has been used in psychophysiological studies in normal volunteers and patients with severe mental disorders including major depressive disorder and PTSD (with similar doses to those used in our proposed study) safely for three decades. Furthermore, the s-enantiomer of ketamine was approved for use as an adjunctive treatment for major depressive disorder by the Food & Drug Administration, and more recently for the treatment of depressive symptoms in individuals with major depressive disorder with acute suicidal ideation or behavior, reflecting its favorable risk versus benefit profile. Perceptual disturbances may 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-lived, resolving several minutes following the end of infusion. Other side effects commonly associated with ketamine include temporary increases in blood pressure and/or heart rate which will be monitored closely during, and for 1 hour after the end of, the infusions. Use of ketamine may also be associated with nausea. Interruption or discontinuation of infusion is usually adequate to resolve these ketamine-associated acute side effects.

Risks associated with WET:

Although WET may decrease PTSD and related symptoms, we recognize that individuals with PTSD may face the risk of symptomatic worsening. Indeed, one concern with exposure to trauma reminders is that individuals may acutely feel more anxious, even though exposure and habituation generally decrease PTSD symptoms over time. Conducting WET remotely via video telehealth requires special care in monitoring potential symptom worsening during sessions. We will take multiple precautions to ensure patient safety.

Financial risks:

Subjects will not be charged for any study procedures. However, in case they experience an adverse effect and seek care, they or their insurance provider will be responsible for this clinical care. Subjects will be informed of this risk as part of informed consent process.

2.3.2 KNOWN POTENTIAL BENEFITS

All study subjects will be informed that there may not be any benefit to them individually as a result of taking part in the study. All study subjects will receive without cost an extensive psychiatric and medical evaluation, which may be of potential benefit to the subjects. Furthermore, participants may experience improvement in symptoms, including PTSD and co-morbid depressive symptoms, with ketamine infusions and WET.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

There are three areas in which safeguards to protect subjects from undue risk require discussion. These include the procedures used to obtain informed consent, the procedures used to ensure confidentiality of the subjects' data, and the procedures used to minimize possible risks associated with the study procedures. In the consent form, and in discussion with an investigator, subjects are advised fully of the procedures to be used, the amount of time required of them, the possible risks and benefits of the procedures, their right to refuse participation in the study without prejudice, their right to terminate participation at any moment without prejudice, and the name and telephone number of the Principal Investigator. In the informed consent form, subjects are told that the information they provide and all findings will be kept strictly confidential, with access limited to the research staff and the possible exception of state or federal regulatory personnel. Only the PI and the clinical research coordinator will have access to the code which links that participant study ID number to protected health information. This information will be kept on a password-protected computer on the ISMMS campus and backed up on a protected ISMMS server that is maintained by IT personnel and designed to house confidential patient information. The electronic data capture system used to collect data for this proposed study, REDCap (Research Electronic Data Capture), will collect it in a de-identified fashion, using only the subjects' assigned study ID number (after eligibility is verified). As the study requires infusions of ketamine, subjects will be informed that their protected health information may be entered in the electronic medical record system that is used by ISMMS (EPIC). Results from this proposed study will be published as group data without the use of characteristics that would identify individual subjects. We quote information only by number in conference discussions, scientific reports, or publications, in order to maintain anonymity.

We have described above the potential risks of the research procedures and the safeguards that will be used to minimize risks. These include termination of subjects from research participation if it is believed that such participation endangers their welfare. Monitoring procedures are used to evaluate potential side effects of treatment or of research procedures. The protocol stipulates an extensive medical and psychiatric evaluation of all subjects as a condition for research participation. Subjects are monitored throughout the study for potential reactions to psychological assessments, ketamine administration, or participation in WET, including treatment-emergent suicidality. Special attention will be devoted to monitoring and assessing participant safety during remote video telehealth sessions, including monitoring for potential symptom worsening. Any concern about elevated participant risk identified by a clinical rater or study therapist is immediately brought to the attention of the PI or another study-affiliated psychiatrist, who will evaluate the participant further. As is standard for our Center, a physician is on call at all times between clinic visits so that adverse reactions can be evaluated.

Suicidal Ideation and Imminent Harm: Despite treatment, participants may get worse or become withdrawn and uncommunicative. In these cases, it is helpful and potentially lifesaving for doctors to have access to a family member or friend who can inform them of the subject's condition. To ensure safe participation, it is helpful to ask each subject to designate an emergency contact person. All suicide threats are taken seriously. It is important to assess the risk of suicide carefully when working with these patients. Due to these reasons, as part of the informed consent process, all participants will be asked to identify an emergency contact person, provide their contact information and complete a release of information form so that the study team may contact these individuals in case of an emergency.

Many subjects may admit to fleeting thoughts of death or briefly wishing for death; these thoughts need to be considered in context of the subject's overall history, along with a consideration of other risk factors for suicide. Study psychiatrists will assess every patient at each visit for suicide risk and potential. As is the SOP for our Center, a 24-hr on call psychiatrist (PI or study-affiliated psychiatrist) will be designated to cover emergencies. Individuals at such risk will be treated appropriately, including options such as increased contact, more frequent clinical visits, or emergency psychiatric hospitalization. Please note that subjects who score 4 or more on the past-month suicidal ideation module of the C-SSRS or had any suicidal behavior within the past month on the CSSRS at screening will be excluded. Our Center, and the PI, have extensive experience working with individuals with elevated risk of suicide and maintaining the safety of individual subjects.

Incidental findings: For laboratory tests, all results will be reviewed by the PI or study-affiliated psychiatrist, and any incidental finding will be conveyed to the subject with provision for additional work-up if needed.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To evaluate the efficacy of adding WET to ketamine therapy in improving PTSD symptoms from baseline to 12 weeks from the start of WET, in individuals with chronic PTSD.	Change in PTSD symptom severity, as assessed with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), between baseline and 12 weeks following the start of WET.	*The CAPS-5 is the gold-standard outcome measure in clinical trials in patients with PTSD. Timing and duration of primary outcome assessment*

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		were selected based on findings from prior WET and repeated ketamine studies.
Secondary (Exploratory)		
To evaluate longitudinal change in PTSD and depressive symptoms (and clinical global impression and psychosocial functioning) following administration of ketamine infusions and WET, as well as the relationship between change in PTSD and depressive symptoms. All participants will be followed for 12 weeks from the start of WET. To capture any ketamine-related rapid changes in PTSD and depressive symptoms	Change in PTSD symptom severity from baseline to 6 weeks, using the CAPS-5; change in PCL-5, MADRS, CGI, and SDS from baseline to 6 weeks, and from baseline to 12 weeks; in patients with maintained PTSD symptom improvement after 12 weeks, change in PTSD symptom severity from baseline to 16, 20, and 24 weeks. Change in IES-R and QIDS-SR, with 24-hour recall, from baseline to 24 hours after the first infusion, at each infusion day, and 24 hours after the fourth infusion.	*The CAPS-5 is the gold-standard outcome measure, and the PCL-5 is a self-report measure commonly used in clinical trials for PTSD. The MADRS (depressive symptoms), CGI (clinical global impression), and SDS (psychosocial functioning) are commonly used as well.* *These scales are commonly used in clinical trials, including in our 2 previous clinical trials of ketamine for PTSD to capture rapid symptom improvement.*
To evaluate whether ketamine-induced change in extinction learning predicts PTSD symptom improvement from baseline to 12 weeks from start of WET.	Performance on Extinction Learning Task following ketamine infusions.	*The computerized Extinction Leaning Task is sensitive to PTSD. Assessment time point after four infusions (compared to baseline) allows for assessment of maximal change in extinction learning prior to adding WET to ketamine treatment.*

4 STUDY DESIGN

4.1 OVERALL DESIGN

The main objective of this study is to evaluate the efficacy of adding WET to a course of ketamine infusions in improving PTSD symptoms from baseline to 12 weeks from the start of WET, in individuals with chronic PTSD (Aim 1). Additional objectives are to evaluate whether ketamine-induced change in extinction learning, assessed with an online Extinction Learning Task, predicts PTSD symptom improvement (Aim 2) in participants with chronic PTSD. In order to accomplish these objectives, we will conduct an open-label trial of ketamine plus WET in individuals with chronic PTSD. Participants will start WET after completing the first four ketamine infusions. Participants will receive two additional ketamine infusions (for a total of six infusions), interwoven with five WET sessions.

Eligible participants will receive a total of six ketamine infusions (see Figure 1 and Methodological Details below), administered over 2 consecutive weeks,[49] and will also begin WET sessions. The first 2 WET sessions will be administered interleaved with the last 2 ketamine infusions, on different days. The last three sessions of WET will be administered during the week following the end of ketamine infusions.

The clinical trial primary outcome is change in PTSD symptom severity from baseline to 12 weeks from the start of WET, measured with the CAPS-5[50]. Secondary outcomes include change in PTSD symptom severity from baseline to 6 weeks from the start of WET, and change in other outcome measures from baseline to 6 weeks, and baseline to 12 weeks. Patients whose improvement in PTSD symptoms is maintained after 12 weeks will complete monthly assessments up to 24 weeks from start of WET. A continuous clinical rater will administer the CAPS-5 and the MADRS for the primary and secondary outcome assessments.

Methodological Details

a. Screening Procedures (see **3.1 Schedule of Activities**)**:** Individuals will undergo informed consent procedures and study screening at the clinical site. If the COVID-19 pandemic remains a concern, these procedures will be conducted remotely, via a HIPAA-compliant telehealth platform (e.g., VSee, Doximity, HIPAA-Zoom). After signing the informed consent form, participants will complete a structured diagnostic interview with the SCID-5,[51] the CAPS-5 to determine PTSD symptom severity,[50] the MADRS to determine depressive symptoms severity,[52,53] the Wechsler Test of Adult Reading (WTAR),[54] and the Montreal Cognitive Assessment test (MoCA).[55] Please see **3.1 Schedule of Activities** for a complete list of scales to be completed by study participants at screening. All subjects will complete forms related to demographics, medical history, concomitant medications and treatment, and self-report measures including the Childhood Trauma Questionnaire (CTQ),[56] Traumatic Life Events Questionnaire (TLEQ),[57] PTSD Checklist for DSM-5 (PCL-5),[58] and Sheehan Disability Scale (SDS).[59] Participants will also undergo a medical evaluation, including medical history; physical examination by a nurse practitioner; documentation of height, weight and vital signs; comprehensive blood tests; and urinalysis, urine toxicology screen, and urine pregnancy test (in women of childbearing potential). After reviewing all information, the PI or other study psychiatrist will meet with each patient to review their psychiatric and medical history, and current medications and treatment, answer any questions the patient might have,

administer the Columbia Suicide Severity Rating Scale (C-SSRS)[60] and the CGI-S,[61] document contraceptive use, and verify patient eligibility for the study. If a participant is taking any exclusionary psychotropic medication listed in the exclusion criteria, the prescribing psychiatrist or other prescribing physician must taper the participant off the medication, in consultation with the study PI or other study psychiatrist, if it is determined that the medication is of no clinical benefit to the individual.

b. Administration of ketamine infusions: Eligible participants will receive a total of six infusions, administered over two consecutive weeks. At each infusion, they will receive 0.5 mg/kg of racemic ketamine hydrochloride, and total dose no higher than 60 mg per infusion (regardless of body weight). All infusion procedures and monitoring will take place at the Icahn School of Medicine at Mount Sinai (ISMMS) Psychiatry Infusion Suite or Clinical Research Unite (CRU) using the existing Standard Operating Procedures that are in place for the administration of ketamine in research studies.

c. Assessment of response to ketamine: Response to ketamine, assessed 24 hours after the fourth infusion, is defined as ≥ 30% reduction in PTSD symptom severity on the CAPS-5, administered to the participant by a trained clinical rater, compared to baseline (prior to any infusions). This degree of improvement is commonly used in clinical trials in individuals with PTSD to represent clinically significant PTSD symptom improvement,[62-64] and was also employed in our completed RCT of repeated ketamine for PTSD.[8]

d. WET Sessions:

WET consists of five sessions, with the first session lasting 1 hour and each subsequent session lasting approximately 40 minutes. The first session includes psychoeducation about common trauma reactions and the treatment rationale, presented by the therapist. The participant is then given general instructions for completing the trauma narratives and specific instructions for completing the first 30-minute narrative writing during that first WET session. All WET sessions begin with the therapist reading the specific writing instructions, clarifying any questions the participant might have, and leaving the instructions with the participant during the 30-minute writing session. Writing instructions begin with a focus on the details of the trauma and then shift to the meaning of the trauma event. After 30 minutes of writing, the therapist stops the writing and conducts a 5-10 minute check-in regarding how the writing session went for the participant.

All participants will be administered WET, beginning after they complete the first four infusions. WET will be delivered remotely by therapists to participants in their homes, via a HIPAA-compliant video telehealth platform, using methods implemented before the COVID-19 pandemic and further developed during the pandemic by study consultant Dr. Denise Sloan, who co-developed the WET intervention.[65] Therapists will be Master's- or PhD-level mental health providers, supervised by Dr. Sloan. WET will be delivered over a total of two weeks. The first two sessions of WET will be delivered starting after completion of the first four ketamine infusions, and interleaved with the last 2 ketamine infusions (each WET session and ketamine infusion occurring on one of four different days). The ketamine dose and administration protocol will be the same for all six infusions. The last three sessions of WET will be delivered the following week, after completion of the six ketamine infusions. Participant narratives will be collected as part of the WET sessions, as they are a necessary part of treatment and are used to ensure that the instructions for each writing session are followed by the participants. Collection will be completed securely, either by uploading a picture of the narratives to the REDCap database, uploading a scanned copy of the narratives, or by participants delivering the narratives in person (if there is a planned in-person visit shortly thereafter) or by mail.

e. Assessments and Outcome Measures (please see **3.1 Schedule of Activities** for additional details)**.** Assessments will be administered weekly starting at baseline, prior to the first infusion.

Primary outcome measure: The Clinician-Administered PTSD Scale (CAPS-5),[50] the gold standard measure in clinical trials in individuals with PTSD, will be administered weekly by a blinded clinical rater. The primary outcome is change in PTSD symptom severity as measured by the CAPS between baseline and 12 weeks following the start of WET. All participants will be followed for 12 weeks. Participants who remain improved will additionally be followed monthly for 12 to 24 weeks.

Secondary outcome measures (exploratory)**:** The CAPS-5 will be administered weekly (beginning at baseline prior to the first ketamine infusion) until 6 weeks from the start of WET; thereafter, the CAPS-5 will be administered weekly as tolerated until 12 weeks; all participants will be administered the CAPS-5 at the 12-week time point. Participants who maintain PTSD symptom improvement after 12 weeks will be assessed monthly up to 24 weeks from the start of WET or until loss of improvement, by the blinded clinical rater. The PCL-5 and SDS (self-report scales), the MADRS (administered by the blinded clinical rater), and the CGI-S and CGI-Improvement scales (administered by a study psychiatrist or clinician) will be administered at the same time points until 12 weeks, and then monthly up to 24 weeks or until loss of improvement (See **3.1 Schedule of Activities**). The Quick Inventory of Depressive Symptomatology-Self-Report version (QIDS-SR)[66] and the Impact of Events Scale-Revised (IES-R),[67] both self-report scales, will be administered at baseline, 24 hours after the first infusion, at each infusion visit, and on the day of response to ketamine assessment, to capture any ketamine-related rapid changes in symptom levels. An abbreviated version of the Medical Outcomes Study Social Support Survey (MOS-SSS),[68] the Centrality of Event Scale (CES),[69] and the Perceived Ability to Cope with Trauma Scale (PACT)[70] will be administered at baseline (prior to any infusions) and again 3 weeks after the first WET session; data from these scales will be used for Aim-3 analyses.

Safety Assessments: Participants will be evaluated prior to each infusion by the PI or another study-affiliated psychiatrist; including review of vital signs, weight/BMI, drug and pregnancy tests, concomitant medications and adverse events. Participants will be monitored continuously during all ketamine infusions. On infusion days, side effects will be assessed with the Patient-Rated Inventory of Side Effects (PRISE) Adverse Event Visit Checklist,[71] the Clinician-Administered Dissociative States Scale (CADSS),[72] the Brief Psychiatric Rating Scale (BPRS) 4 items assessing positive symptoms,[73] and the Young Mania Rating Scale first item.[74]

f. Online Extinction Learning Task (see **Figure 7 :** The computerized task, administered online, consists of three phases: an initial aversive conditioning phase (in context A), extinction learning phase (in context A), and further extinction learning (in novel context B) (see **Figure 6**). Importantly, the conditioned stimulus (CS) associated with the aversive loss outcome (US), the CS+, is only partially reinforced (P(US|CS+)=1/3), and the transition to extinction (P(US|CS+)=0) is unsignaled. This design maximizes uncertainty about whether CS+ trials during extinction should be grouped with unreinforced conditioning phase CS+ trials, implying a common cause is responsible for both kinds of observations, or instead that the change in contingencies indicates it is likely that a new cause is active in the environment. The predictive measure generated from this task for Aim 2 analyses is the *difference in discrimination between CS+ and CS-* across the first six blocks of the task. Further, loss expectancy ratings data from each trial of the online extinction task will be analyzed via a computational model of latent cause inference developed by Gershman, Niv, and colleagues[75,76] (see **Data Analysis Strategy**). There are *two versions of the task* (see **Figure 7** note): one version will be administered prior to any ketamine infusions, and the second version

after completion of the first four infusions. We will examine whether ketamine-induced improvement in extinction learning is associated with improvement in PTSD symptoms from baseline to 12 weeks from start of WET.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Preliminary Data:

RCT of repeated IV ketamine for PTSD. Following our initial proof-of-concept RCT of single-dose IV ketamine infusion in patients with chronic PTSD,[6] we completed the first RCT of repeated IV ketamine infusions in individuals with chronic PTSD (six infusions over two consecutive weeks), compared to repeated IV infusions of the psychoactive placebo midazolam (n=30). Participants' primary trauma ranged from assault to the WTC attacks/recovery work, and PTSD duration averaged 15 years. Results revealed a robust, large-magnitude improvement in PTSD symptom severity in the ketamine group from baseline to

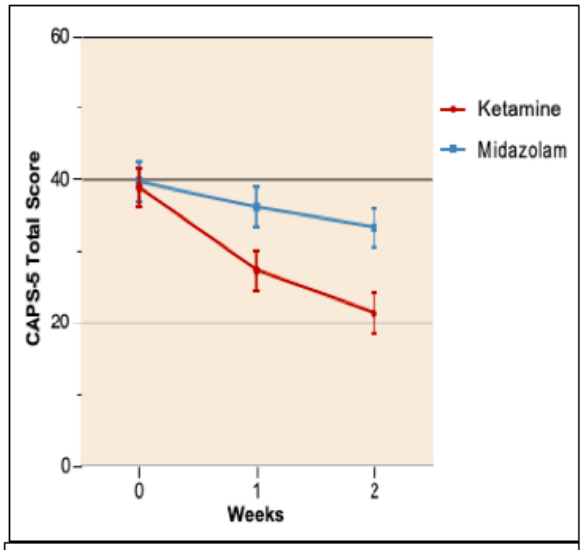


Figure 3. Effect of Treatment with Ketamine (vs. Midazolam) on PTSD Symptom Severity[10]

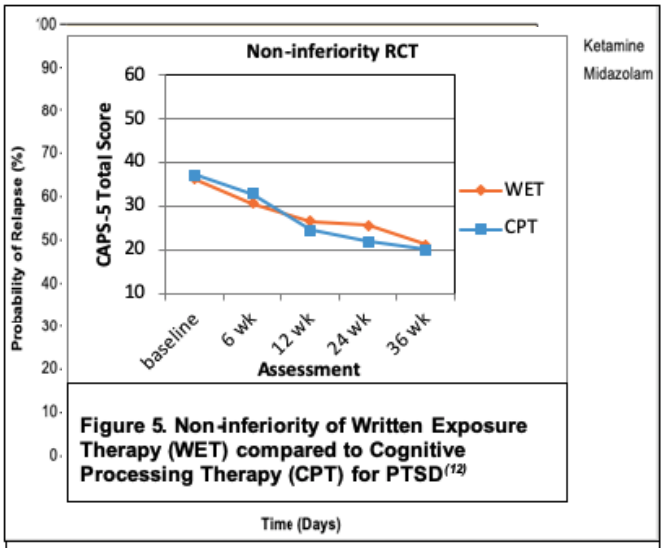


Figure 5. Non-inferiority of Written Exposure Therapy (WET) compared to Cognitive Processing Therapy (CPT) for PTSD[12]

Figure 4. Risk of Loss of Response among Responders to Ketamine and Midazolam Infusions in PTSD[10]

week 2, compared to the midazolam group, assessed with the CAPS-5 (F=5.97, df=2, 55, p=0.0045, d=1.13).[8] In the ketamine group, the CAPS-5 total score was 11.88 (SE=3.96, p=0.004) points lower (d=1.13, 95% CI=0.36-1.91; see **Figure 3**); 67% of participants were treatment responders, defined as ≥ 30% improvement from baseline on the CAPS-5, compared with 20% in the midazolam group (χ^2=4.89, p=0.03).[8] Ketamine infusions were additionally associated with significantly greater improvement in co-morbid depressive symptoms from baseline to 2 weeks, assessed with the Montgomery-Åsberg Depression Rating Scale (MADRS; F=5.68, df=2, 55, p=0.006, d=0.92), and on a global measure of clinical improvement, the Clinical Global Impression Severity Scale (CGI-S; F=5.19, df=2, 50, p=0.009). In participants who responded to ketamine, median time to loss of response was 27.5 days after the 2-week primary outcome assessment day (see **Figure 4**), motivating the proposed study, investigating a novel approach aimed at maintaining symptom improvement over time by adding a brief and scalable exposure-based psychotherapy to a course of ketamine infusions delivered with the same schedule of six infusions over two consecutive weeks, which was associated with rapid and robust symptom improvement in individuals with chronic PTSD in our completed RCT.[8]

Development of Written Exposure Therapy. In NIMH-funded studies, Co-Investigator Dr. Sloan and colleagues have demonstrated the efficacy of WET in reducing PTSD symptom severity,[39-41] including an NIMH-funded RCT (R01MH095737) that demonstrated WET's non-inferiority to CPT,[41] one of the two therapies with highest evidence base for the treatment of PTSD (see **Figure 5**). Of key relevance to the proposed RCT, greater physiological activation in response to written exposure during the first session was found to significantly predict symptom improvement from WET, suggesting that fear extinction learning is a mechanism underlying improvement in PTSD with WET.[34,35] If ketamine infusions in

individuals with chronic PTSD enhance extinction learning, a mechanism thought to underlie WET, the addition of WET might result in enhanced PTSD symptom improvement through a synergistic effect.

Online Extinction Learning Task: Study in WTC Workers and Survivors with and without PTSD. Our research team developed the online Extinction Learning Task proposed for Aim 2 of this study, led by postdoctoral fellow Dr. Agnes Norbury.[48] This behavioral extinction learning paradigm consists of three phases: (1) initial aversive conditioning phase, in context A; (2) extinction learning phase, also in context A; and (3) further extinction learning, in new context B (see **Figure 6**). Participants are told that they are traveling through different zones of a spaceship. In order to power their trip home, they need to escape with enough space coins. These coins are carried by helper robots, but some are unreliable. Participants are asked to rate (sliding bar), on each trial, how likely they think that particular robot would be to lose the coins it is carrying. ***Task sensitivity to PTSD status:*** Pilot data were collected for *N*=48 adults with DSM-5 criterion A trauma exposure to the World Trade Center (WTC) disaster (WTC responders and survivors; mean age 53 ± 7.0, *N*=16 female). *N*=34 (71%) participants currently met DSM-5 criteria for WTC-related PTSD (mean PCL-5 total score 44.1 ± 8.6), and *N*=14 (29%) participants were highly resilient to WTC-related exposures (no current or lifetime diagnosis of PTSD or other DSM-5 Axis-I disorder; mean PCL-5 total score 1.6 ± 1.7). An earlier version of the online Extinction Learning Task that we propose to use in this study was administered to all participants. Behavior on the Extinction Learning Task differed between the PTSD and Resilient groups (repeated-measures ANOVA of loss-expectancy ratings with within-subjects factors of conditioned stimulus [CS] type, task stage, and clinical group, using Tukey-LSD correction for multiple comparisons in follow-up contrasts). Specifically, there was a significant CS x group interaction ($F_{1,806}$=12.6, p<0.001) –driven by a tendency towards higher overall loss prediction ratings for CS- stimuli (less discrimination between CS+ and CS- stimuli) in symptomatic individuals (mean difference in CS- rating PTSD *vs* resilient 13.8 [SE 5.7], 95%CI -1.3–28.9, p=0.08; difference in CS+ rating PTSD *vs* resilient 2.1 [SE 5.7], p>0.9). Discrimination between CS+ and CS- stimuli across the first six blocks of the task differed between the groups [t_{34}=-2.02, p=0.051, mean discrimination (difference in loss expectancy ratings) in the PTSD group=20.1, in the Resilient group=35.6 (points on a scale 0-100), Cohen's d = 0.57. Computational latent cause modeling in this study showed that higher PTSD symptom severity, and specifically higher

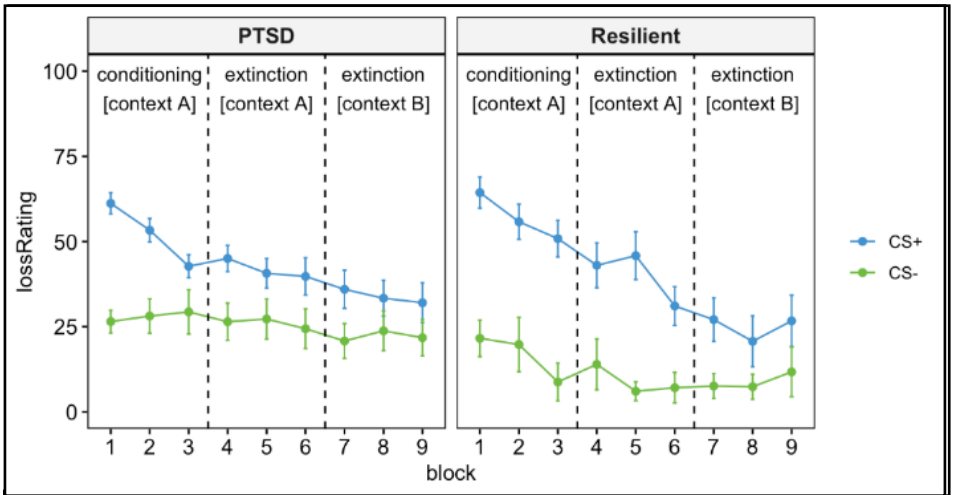


Figure 6. Loss expectancy ratings on the extinction task by conditioned stimulus (CS) type and task stage, by clinical group (PTSD, Resilient). Data is represented separately for WTC-exposed individuals who met criteria for WTC-related PTSD (*N*=34), and resilient individuals who were exposed to criterion A trauma during the WTC disaster but never met diagnostic criteria for PTSD (*N*=14). Error bars represent standard error of the mean. CS+,

severity of intrusion symptoms, was associated with the belief that the same underlying cause explains events observed during conditioning and extinction stages of the task.[48]

For Aim 2, extinction learning will be measured twice, with two versions of the online Extinction Leaning Task: *(1)* before the first ketamine infusion and *(2)* after completion of four ketamine infusions (pre-WET). Extinction learning will be defined as the difference in discrimination between the aversively conditioned (CS+) and safe (CS-) stimuli on the first six blocks of this task. Ketamine-induced change in extinction learning will be evaluated as a predictor PTSD symptom improvement from baseline to 12 weeks from the start of WET. A recently developed computational model[75,76] will be employed to determine whether differences in discrimination between CS+ and CS- are related to differential inferences about the causal structure of the task during learning (i.e., participants' belief that one vs. multiple underlying causes explain observations during progression through the task).[48]

4.3 JUSTIFICATION FOR DOSE

In this trial, the dose of ketamine administered at each infusion (0.5 mg/kg, administered over 40 minutes) is the same dose that is administered in most clinical trials of intravenous ketamine for treatment-resistant depression (TRD), and the same dose that was administered in our two completed clinical trials of intravenous ketamine for chronic PTSD. This dose has shown efficacy and safety for these disorders. Additionally, as requested by the FDA for safety reasons, the maximum dose of ketamine will be 60 mg at each infusion, regardless of participant body weight.

Employing the same dose, frequency, and total number of infusions in this open-label clinical trial of ketamine + WET will allow us to compare study findings to the findings from our completed clinical trial of repeated ketamine infusions for PTSD, which evaluated the efficacy of a repeated course of ketamine infusions, without WET.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study shown in the Schedule of Activities (SoA), Section 1.3. For all participants, the earliest end of study will be the 12-week follow-up assessment. For participants who remain improved at this 12-week assessment, the end of study will be their final follow-up visit (depending on time to loss of this improvement).

5 STUDY POPULATION

5.1 INCLUSION 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-5, and a past-month total CAPS-

5 score ≥ 30 at screening – 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. Men who are sexually active with women of childbearing potential must use a medically accepted reliable means of contraception and must agree not to donate sperm for a period of 90 days after receiving the last dose of ketamine;
7. 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).

5.2 EXCLUSION CRITERIA

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 uncorrected hypothyroidism or hyperthyroidism, as indicated by a TSH value 25% above or below the normal range;
6. A Body Mass Index (BMI) >40;
7. Hormonal treatment (e.g., estrogen) started in the 3 months prior to the first infusion day;
8. History of a neurodevelopmental disorder (e.g., autism, pervasive developmental disorder) ;
9. History of one or more seizures without a clear and resolved etiology;
10. Lifetime history of bipolar I or II disorder;
11. Presence of psychotic symptoms, or diagnosis of a lifetime psychotic disorder including schizophrenia or schizoaffective disorder;
12. Drug or alcohol use disorder within the preceding 3 months;
13. Previous recreational use of ketamine or PCP on more than one occasion, or any recreational use of ketamine or PCP within the last two years;

14. Previous non-response to clinical or research ketamine or esketamine administration;
15. Current diagnosis of bulimia nervosa or anorexia nervosa;
16. Patients judged clinically to be at serious and imminent suicidal or homicidal risk;
17. SBP >165 and DBP >95 at infusion days – higher BP allowed to account for stress or anxiety;
18. Concurrent treatment with opioid medication, or with long-acting or daytime short-acting benzodiazepines within two weeks of study start;*
19. Current cognitive impairment, as defined by a score <23 on the Montreal Cognitive Assessment (MoCA);
20. Estimated IQ <80;
21. Currently receiving evidence-based psychotherapy for PTSD (e.g., prolonged exposure, cognitive processing therapy);

Note: Concurrent treatment with other psychotropic medications (including a short-acting benzodiazepine at bedtime only) will be permitted, but dose must be stabilized for at least three months before study start.

* 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 taper a potential participant off of a medication; rather, this may only be completed by the prescribing physician. This is our policy across all of our studies.

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Participants will be asked to refrain from eating anything or drinking any non-clear liquids starting at midnight the night before each infusion.
- Inform the study team of any changes in their medications or psychotherapy regimen.
- Refrain from taking short-acting benzodiazepines during daytime.
- Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of an exclusionary concomitant medication, or a recent change in medications or psychotherapy may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Planned Recruitment Activities:
The research strategy for the present study calls for the enrollment of N=30 adults with chronic posttraumatic stress disorder (PTSD), aged 18-70 years. This enrollment is with the goal of identifying up to N=16 participants who are screened, eligible, and go on to receive ketamine infusions and WET. This is based on an anticipated screen fail rate of 25% to 50%.This enrollment will take place over the proposed 54-month recruitment period.

The expected enrollment rate of ~1.2 subjects per month who receive ketamine infusions is highly feasible based on the current flow of subjects in clinical trials at the Depression and Anxiety Center for Discovery and Treatment (DAC) and the demonstrated track record of similar rates in prior studies at DAC and recruiting from WTC populations in CDC/NIOSH-funded studies led by PI Dr. Feder. As one of the major research and clinical programs at the Department of Psychiatry at the Icahn School of Medicine at Mount Sinai (ISMMS), DAC has five full-time faculty members. This includes three psychiatrists, two part-time clinical psychologists, two full-time post-doctoral fellows, three full-time Masters-level clinical raters, five full-time clinical research coordinators, a database manager, and a program administrator. Investigators at DAC have a long track record in successfully recruiting subjects and completing studies involving the assessment and treatment of individuals with PTSD.

Recruitment Procedures:

We will post advertisements on Craigslist, ResearchMatch, Facebook, TrialFacts, BuildClinical and Google and will post flyers in the community, and accept referrals from clinicians. Through TrialFacts and BuildClinical, we will have targeted advertisements on Google and Facebook.

Potentially eligible participants who express interest in being considered for this clinical trial will complete a phone screen interview under the supervision of PI Dr. Feder. The PI will review subject enrollment at weekly project meetings with the primary study coordinator and Co-Investigators Drs. Jha and Murrough, so that any deviation from the anticipated enrollment schedule will be detected and remedied quickly. All outreach and advertising activities will also be reviewed on a weekly basis.

Engagement Strategies for Retention:

The PI will hold weekly project meetings with the study coordinator and Co-Investigators Drs. Jha and Murrough to monitor enrollment and ensure that enrolled subjects are completing all study procedures as per protocol.

For infrastructure, the Scientific Computing department at ISMMS provides a secure centralized electronic data management platform that is HIPAA and FDA-compliant – Research Electronic Data Capture (REDCap). For this specific project, we will create databases in REDCap for screening, subject tracking, and a study database proper. As subjects complete study visits, the date of each visit will be entered in the database. Missed visits will be coded for reason (such as scheduling issues, illness). On a weekly basis, the primary research coordinator, who will also serve as data manager, will run a report on patient enrollment and study progress for review by the PI. On an ongoing basis, the data manager, PI,

and Co-Investigators Drs. Murrough and Jha will review the status of patient accrual and retention, as well as study case report form completion, to identify and resolve bottlenecks or problem areas that arise. Dr. Feder will additionally meet regularly with the study therapists, and work together with Dr. Denise Sloan (who will supervise the study therapists) to identify any potential issues related to delivery of WET to participants.

Within DAC, the study coordinator will be the participant's point of contact during the study. Subjects will be provided with phone and email contact information for their coordinator, in addition to contact information for the PI. When enrolled, participants will provide detailed contact information for themselves, their clinical providers (if applicable), and a family member or close friend who is aware of the participant's study participation. At each visit, the study coordinator will "check in" with the participant regarding protocol adherence and study satisfaction, in addition to any protocol-specific procedures. This system provides an opportunity to detect reasons for non-adherence or early discontinuation in a timely fashion and to address any issues, if at all possible.

Strategies to ensure a diverse, representative sample:

Since its inception, ISMMS has fostered community partnerships that are mutually beneficial to the School and nearby underserved populations. Faculty members have benefited from collaborations with underserved and often hard-to-reach populations and front-line clinicians, to recruit for research, develop research partnerships and to ensure that community expertise, experiences and priorities inform their work. The Centers for Community and Academic Research Partnerships (CCARP) at Mount Sinai is facilitating the formation and transformation of these partnerships so that they become the catalyst for groundbreaking research that uncovers and addresses important social, environmental, and health problems; builds skills among academic and community partners; and improves health of communities.

The ISMMS is part of a large urban medical center, located in the Manhattan borough of New York City, and benefits from a large and diverse catchment area. For the proposed clinical trial there are no special restrictions with regard to ethnicity or race. It is expected that the study sample will closely approximate the racial and ethnic composition of populations residing in the New York City metropolitan area.

Potential recruitment/enrollment challenges and strategies that can be implemented in the event of enrollment shortfalls:

Anticipated barriers include issues with staff workload and scheduling windows. This will be addressed by the use of back-up coordinators for the primary study coordinator on the proposed project. Furthermore, Co-Investigators Dr. Jha, Dr. Murrough, and Dr. Klein will serve as back-up study physicians for the PI, Dr. Feder, within the research team. Back-up team members will allow the team to screen and enroll participants and complete study visits within participant's availability. All study staff involved in participant recruitment will be trained by the PI, in collaboration with Director of DAC Dr. Murrough, and participant progress and study procedures will be reviewed at weekly project meetings to ensure protocol adherence and consistency of procedures across primary and back-up study personnel.

Anticipated participant-related barriers include appointment scheduling, transportation issues, and maintaining contact between study visits. To ensure that participants are able to attend appointments,

the visit schedule will allow for flexibility. To help address transportation issues, the study team will offer patients metro cards and other transportation resources available through DAC, including a car service to take participants home on the days of their ketamine infusions. Research staff will discuss contact methods with each participant during screening in order to establish multiple methods of contact, along with preferred contact methods to maintain contact between appointments. Research staff will check voicemail and email daily in order to be able to respond to patient contact. Staff will also reach out before each scheduled appointment to ensure participants are able to attend and complete visits as scheduled. To ease the burden on participants, we will also administer the five WET sessions remotely, via a HIPAA-compliant video telehealth platform.

At the current moment, the COVID-19 pandemic poses a potential barrier to enrollment in this and other studies. DAC is working closely with Departmental and Health System leadership to ensure optimization of SOPs related to mitigating risks pertaining to COVID-19 infection. Strategies to mitigate this barrier include the use of clear and consistent messaging to potential participants regarding safety precautions at DAC, including the implementation of thorough and consistent hospital-grade cleaning and disinfecting, the use of masks and eye protection by study personnel, the use of masks by participants, and social distancing. We are also allowing provisions for remote visits (via HIPAA-compliant video telehealth platforms) wherever possible, in addition to the WET sessions, which will take place remotely.

In the case of slower than anticipated enrollment, PI Dr. Feder and Co-Is Drs. Murrough and Jha will review reasons for pre-screen and screen failures during weekly DAC research meetings, and consider additional recruitment and outreach methods including additional advertising methods, and additional outreach methods to clinicians and centers providing treatment to individuals with chronic PTSD.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Ketamine:

Ketamine is widely available as an anesthetic agent under the brand name Ketalar, for use in emergency rooms and hospital settings for sedation and analgesia. The typical sub-anesthetic dose in clinical trials for patients with TRD or PTSD is 0.5 mg/kg, administered intravenously over 40 minutes.

Relevant to the criteria for an exemption in § 312.2(b), we informally reached out to the Food and Drug Administration (FDA) via email seeking their advice regarding the IND exemption. We were informed that the Division of Psychiatry Products is currently exempting studies with 3 or fewer intravenous infusions of subanesthetic doses of ketamine. As our proposed project involves 6 infusions, we will proceed with an IND submission. The PI, Dr. Feder, and Co-Is Drs. Murrough and Jha have extensive

experience in obtaining IND exemptions for ketamine trials. No subject will be enrolled in the proposed study until an IND exemption has been granted.

Relevant to the individual criterion for exemption in § 312.2(b) (bolded statements from FDA guidance):

1. **The drug product is lawfully marketed in the United States.** We propose to use ketamine that is commercially available and will be supplied by our research pharmacy, the Investigational Drug Service at the Icahn School of Medicine at Mount Sinai.
2. **The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.** We do not intent to report the results of our proposed study to the FDA as a well-controlled study in support of a new indication, nor do we intend to use it to support any other significant change in the labeling of the drug. As mentioned earlier, the purpose of this study is to evaluate whether the addition of Written Exposure Therapy to a course of ketamine infusions can extend the effect of ketamine on PTSD symptoms in individuals with chronic PTSD who respond to ketamine.
3. **The investigation is not intended to support a significant change in the advertising for the drug.** We do not intend to utilize the data we generate to support any changes in advertising of ketamine. As mentioned in the specific aims section, the purpose of this study is to evaluate whether the addition of Written Exposure Therapy to a course of ketamine infusions can extend the effect of ketamine on PTSD symptoms in individuals with chronic PTSD who respond to ketamine.
4. **The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).** We intend to use ketamine via intravenous route (after diluting it with normal saline for total infusion volume of 100 mL) in adults with PTSD who are medically stable and have no medical contraindications against ketamine administration, three times per week for two weeks (total of 4 or 6 infusions over 2 weeks, depending on ketamine response). Previous reports have used repeated infusions of ketamine (up to 6) over a two-week period, including our recently completed randomized controlled trial of repeated ketamine infusions in patients with chronic PTSD, compared to the active placebo midazolam (PI of the proposed study, Dr. Feder, was the PI of that trial, funded in part by a NARSAD Independent Investigator Award from the Brain & Behavior Research Foundation).
5. **The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).** We plan to enroll subjects after the study is approved by the Institutional Review Board at Mount Sinai and after individual subjects have provided informed consent.
6. **The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).** We do not intend to promote or commercialize the drug product (ketamine) with this investigation.

Written Exposure Therapy:

Written Exposure Therapy (WET) is a brief evidence-based treatment for PTSD, developed by our collaborator and study consultant Dr. Denise Sloan (Boston University). WET will be administered by trained therapists, under the supervision of Dr. Sloan.

6.1.2 DOSING AND ADMINISTRATION

Ketamine:

The dose of ketamine at each infusion is fixed at 0.5mg/kg mg, and up to 60 mg per infusion (regardless of body weight), to be administered intravenously over 40 minutes. Individuals at or above 120 kg will receive 60 mg over 40 minutes. Ketamine infusion will be discontinued earlier if necessary due to side effects as described below:

1. Changes in psychiatric symptoms at any time during the study:
    a. Treatment-emergent mania, hypomania, worsening suicidality or psychosis
2. Emergent medical symptoms on the infusion days:
    a. Criteria for stopping the infusion:
        i. Any change in mental status resulting in inability to respond to verbal stimuli.
        ii. Severe headache, or severe anxiety, or other patient tolerability issues
        iii. SBP >180, DBP >110 on 2 consecutive readings, ~5 min apart
        iv. HR >120 for 5 minutes
        v. RR< 6, SPO2 <90% at any time point
        vi. Should the patient's vital signs deviate from normal, the clinician may temporarily pause the infusion until the vital signs/mental status have returned to normal, and subsequently resume the infusion at the same or slower rate. Recommended protocol: If 150 ml/h not tolerated, slow to 100 ml/h; If 100 ml/h not tolerated, slow to 50 ml/h.
    b. 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 that is not resolved by pausing or slowing the rate of infusion, 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 labetalol will be administered if the response to initial therapy is not adequate.
    c. 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.
    d. 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. 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.

e. In the event that SpO_2 < 95% over 5-minute interval, the study physician will have the option of inserting a nasal cannula or adjusting the 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.
f. In the event of a respiratory or cardiac arrest, Team 7000 will be called.

Procedures Related to Ketamine Administration:

Ketamine Infusion: All infusion procedures and monitoring will take place at the Psychiatry Infusion Suite, Icahn School of Medicine at Mount Sinai (ISMMS), using the existing Standard Operating Procedures that are in place for the administration of ketamine in research studies. All eligible participants will receive **six infusions**, administered three times per week over two consecutive weeks. At each infusion, participants will receive 0.5 mg/kg racemic ketamine hydrochloride, the same dose administered in prior studies of ketamine for the treatment of PTSD [6,49]. An indwelling catheter will be placed in the antecubital vein of the non-dominant 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 administration. Co-Investigator Dr. Jha or another study- affiliated physician with privileges to administer ketamine will be present at the Psychiatry Infusion Suite throughout the administration of ketamine so that potential adverse events can be evaluated and treated promptly. A medical crash cart is available for emergencies. Dr. Jha or another study-affiliated physician will remain available until at least one hour following the termination of the study drug infusion or until the patient meets Aldrete criteria (good respiration, O2 saturation, consciousness, circulation, and activity) for post- anesthesia care, whichever period is longer. Blood samples will be collected from participants during the first infusion for measurement of plasma ketamine and norketamine levels.

Assessment of response to ketamine after four initial infusions: Response to ketamine is defined as ≥ 30% reduction in PTSD symptom severity from baseline (prior to any infusions) determined with the CAPS-5, administered to the participant by a trained clinical rater 24 hours following completion of the fourth infusion. This degree of improvement is commonly used in clinical trials in individuals with PTSD to represent clinically significant improvement,[62,64,77] and was also used in our recently completed RCT of repeated ketamine for PTSD.[49]

WET:

Procedures Related to WET Administration:

WET will be delivered using a structured manual to ensure fidelity. Therapists will be trained Master's- or PhD-level licensed mental health providers, supervised by study consultant Dr. Sloan. WET will be delivered remotely by therapists to participants in their homes, via a secure HIPAA- compliant video telehealth platform, using methods implemented before the COVID-19 pandemic and further developed during the pandemic by Dr. Sloan and colleagues.[65] WET will be administered over a total of 2 weeks. Week 1: The first two sessions of WET will be delivered interleaved with the last two ketamine infusions (each WET session and ketamine infusion occurring on a different day, i.e., four different days). The ketamine dose and administration protocol will be the same for all six infusions. Week 2: The last three sessions of WET will be delivered during the second week post-WET start.

Delivery of WET:

WET will be delivered using a structured manual to ensure treatment fidelity. Therapists will be mental health providers at Mount Sinai. We anticipate that there will be between one and three therapists in this study, who will be assigned to individual participants for the duration of their participation.

WET consists of 5 sessions, with the first session lasting 1 hour and each subsequent session lasting approximately 40 minutes. The first session includes psychoeducation about common trauma reactions and the treatment rationale, presented by the therapist. The participant is then given general instructions for completing the trauma narratives and specific instructions for completing the first 30-minute narrative writing session. All WET sessions begin with the therapist reading the specific writing instructions, clarifying any questions the participant might have, and leaving the instructions with the participant during the 30-minute writing session. Writing instructions begin with a focus on the details of the trauma and then shift to the meaning of the trauma event. After 30 minutes of writing, the therapist stops the writing and conducts a 5-10 minute check-in regarding how the writing session went for the participant.

Training and Supervision of Therapists and Treatment Fidelity:

Following established procedures used clinical trials of WET,[40,41] therapists will be trained and supervised by Dr. Sloan. Therapists will attend a four-hour WET training workshop led by Dr. Sloan, followed by completion of at least two cases of WET supervised by Dr. Sloan that are completed with competency as determined by the supervisor. Therapists will be instructed on data collection during sessions and any required paperwork related to the proposed study. Treatment fidelity will be closely monitored to prevent drift.

Narratives from WET Sessions:

Participant narratives will be collected as part of the WET sessions, as they are a necessary part of treatment and are used to ensure that the instructions for each writing session are followed by the participants. Collection will be completed securely, either by uploading a picture of the narratives to the REDCap database, uploading a scanned copy of the narratives, or by participants delivering the narratives in person or by mail.

Procedures for Transition to Clinical Care at Study Completion:

At the time of initial screening, subjects will be asked to identify if they have a current mental health provider. For patients with a current provider, we will ask them to provide the name and contact information of this provider. Patients who are not eligible for study participation and do not have a current provider will be offered a referral for clinical care if appropriate. For patients who complete the study (including outcome assessments), a study clinician (PI or psychiatrist who is covering for the PI) will meet with them to discuss the transition of care plan. As part of the study exit visit, the study clinician will complete an end-of-study disposition form, which includes a description of the treatment plan and the next scheduled follow-up appointment with their provider, if applicable. This will be

documented in the participant's chart. For patients who have an established psychiatrist or other treatment provider, the study team will work closely to ensure that there is a smooth transition of care from the end of the study to their clinical treatment. A study clinician may contact the participant's primary provider for coordination of clinical care. For patients who do not have pre-established care, the study team will provide referrals to one of the programs currently serving individuals with PTSD, i.e., a referral within the Mount Sinai Health System or larger community, based on availability and patient preference. At the exit visit, the study team will check in on the status of the disposition plan, and any follow-up appointments will be discussed.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The study drug, ketamine, will be acquired, stored, and tracked by the ISMMS research pharmacy, Investigational Drug Services (IDS), in keeping with institutional policies. Full MOPs are available directly from IDS.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

This information will be provided by the ISMMS research pharmacy, IDS.

6.2.3 PRODUCT STORAGE AND STABILITY

This information will be provided by the ISMMS research pharmacy, IDS.

6.2.4 PREPARATION

This information will be provided by the ISMMS research pharmacy, IDS.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

As this is an open-label pilot study, no randomization is required; all eligible participants will receive six ketamine infusions and participate in five WET sessions. No blinding is necessary, as all participants will receive the same treatment.

6.4 STUDY INTERVENTION COMPLIANCE

The primary study monitors, Dr. Feder and Dr. Murrough, will monitor study progress, compliance, 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.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

6.5.1 RESCUE MEDICINE

The study site will supply the following medications, available emergently through the Psychiatry Infusion Suite or Clinical Research Unit or non-emergently through IDS:

- Naloxone (opioid reversal)
- Flumazenil (benzodiazepine reversal)
- Epinephrine, Ephedrine, Phenylephrine
- Esmolol, Metoprolol, Labetalol, Hydralazine
- Atropine
- Albuterol Inhaler
- Lidocaine, Amiodarone
- Hydrocortisone, Diphenydramine
- Aspirin 81mg, Nitroglycerin Tab, Dextrose 25%
- Ondansteron

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from ketamine or WET does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Symptom measures (e.g.,CAPS-5, MADRS, PCL-5, SDS)
- Global Clinical Severity and Improvement (CGI-S and CGI-I)
- End-Of-Infusion labs
- Safety data
- Concomitant medications
- Follow-up plan

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive a total of four or six ketamine infusions, or unable to participate in WET.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Visit Check-list Case Report Form (CRF). Subjects who sign the informed consent form and begin study procedures but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and begin study procedures and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for three scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within one week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Participants in this proposed study will provide the following efficacy data: (A) data from clinician-administered structured interviews (e.g., structured diagnostic interview with the SCID-5 and CAPS-5, clinical evaluation); (B) self-report data (e.g., symptom measures); and (C) behavioral data (online Extinction Learning Task). Additionally, participant will provide data on (D) demographics (e.g., age, sex, race, education, socioeconomic status); (E) measures of estimated IQ and cognitive functioning; and (F) psychiatric history and treatment, including any history of psychiatric hospitalization.

Diagnostic and Assessment Procedures: The diagnostic interviews and clinical ratings will be conducted by Master's- or PhD-level clinical raters well-trained in diagnostic interviews and the clinical rating scales, supervised by the PI. Bi-annual inter-rater reliability procedures are conducted at DAC to ensure adequate calibration of inter-rater reliability (ICC> 0.90). In the event of staff turnover, new raters must achieve this threshold of reliability prior to participation.

The **Structured Clinical Interview for DSM-5 (SCID-5)** is the most widely used structured diagnostic interview to determine psychiatric diagnoses in clinical research settings based on DSM-5 criteria. The SCID-5 is organized into diagnostic modules, to assess mood, psychotic, substance use, anxiety, obsessive-compulsive and related, eating, and trauma- and stressor-related disorders, and other disorders [51]. The SCID-5 will be used in this study to determine whether subjects meet DSM-5 criteria for PTSD and to assess other co-morbid psychiatric diagnoses, in order to determine study eligibility.

The **Clinician Administered PTSD Scale for DSM-5 (CAPS-5)** is a structured diagnostic interview and the gold standard for assessing the DSM-5 symptoms of PTSD. The scale also assesses social and occupational functioning, dissociation symptoms, and the validity of symptom reports. The CAPS-5 uses a single 5-point ordinal rating scale to measure symptom severity. Symptom severity ratings combine information about symptom frequency and intensity obtained by the interviewer. Psychometric properties indicate high criterion and construct validity and high agreement with a self-report measure of PTSD.[50] The CAPS-5 requires approximately 40 minutes to administer. The CAPS-5 will be administered at screening to determine PTSD symptom severity. In addition to meeting DSM-5 criteria for PTSD, subjects must also have a total CAPS-5 score ≥30, indicating at least moderate PTSD symptom severity, in order to be eligible to participate in this study. The CAPS-5 will also be used to determine ketamine responder on non-responder status of participants following the first four ketamine infusions. Importantly, participants' total CAPS-5 severity scores will serve as the ***primary outcome of interest***.

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.[52] 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 MADRS will be used in this study as a secondary outcome measure, to assess change in co-morbid depressive symptom levels over time. Additionally, the MADRS will be employed to assess severity of co-morbid depressive symptoms as a clinical predictor for Aim 3 analyses.

The **Montreal Cognitive Assessment (MoCA)** is a widely used cognitive screening tool to differentiate mild cognitive impairment from cognitive changes associated with health aging.[55] A recommended cutoff score of 23 will be used to determine eligibility for this study, based on meta-analytic findings indicating that the cutoff of 26/30 originally suggested for this measure is associated with a higher percentage of false positives, especially among individuals of lower education or older age.[78]

The **Wechsler Test of Adult Reading (WTAR)** is a neuropsychological assessment measure used to derive a pre-morbid estimate of intelligence, and requires participants to read a list of 50 words.[54] The WTAR will be administered at study screening to estimate participant IQ. Subjects with estimated IQ < 80 will

be excluded from the study. Additionally, estimated IQ derived with the WTAR, used in a prior non-inferiority RCT comparing WET to CPT,[41] will be used as a predictor for Aim 3 analyses.

The **Childhood Trauma Questionnaire (CTQ)** is a widely used, valid and reliable retrospective self-report scale to screen for a history of childhood abuse and neglect. It includes a total of 28 items, and yields five subscale scores –emotional abuse and neglect, physical abuse and neglect, and sexual abuse–, as well as a minimization-denial score.[56] In the proposed study, the CTQ will be employed as a trauma history predictor for Aim 3 analyses.

The **Traumatic Life Events Questionnaire (TLEQ)** is a commonly used and rigorously tested self-report scale to assess the frequency, severity, and timing of a wide range of traumatic experiences experienced across the individual's lifetime, including childhood and adulthood.[57] Lifetime number of traumas, trauma type, and timing will be employed as trauma history predictors for Aim 3 analyses.

The **PTSD Checklist for DSM-5 (PCL-5)** is a widely used 20-item self-report measure to assess the 20 DSM-5 PTSD symptoms.[58] The PCL-5 measure has a Specific version to assess severity of PTSD symptoms in relation to a specific trauma. The Specific version of the PCL-5 will be used in this study as an additional, secondary outcome measure of PTSD symptom severity.

A 5-item abbreviated version of the **Medical Outcomes Study Social Support Survey (MOS-SSS),**[68] a widely used self-report scale assessing perceived social support, including emotional/informational, tangible and affectionate support, utilizing a 5-point Likert scale. This scale will be administered at baseline (before the first infusion) and again 3 weeks after the addition of WET. This scale will be used for exploratory analyses for Aim 3.

The **Perceived Ability to Cope with Trauma (PACT)**[70] is a 20-item self-report scale assessing perceived coping abilities following a traumatic event. There are two main subscale scores: Forward-focused Coping score, reflecting the respondent's ability to maintain goals and plans following a traumatic event, and Trauma-focused Coping score, reflecting the respondent's ability to face feelings and cognitions relating to a traumatic event. Additionally, a Flexibility score can be calculated to determine the respondent's ability to engage in both forward-focused and trauma-focused coping strategies following a traumatic event. This scale will be administered at baseline (before the first infusion) and again 3 weeks after the addition of WET. This scale will be used for exploratory analyses for Aim 3.

The short-item **Centrality of Event Scale (CES)**[69] is a 7-item scale that measures how central the most stressful/traumatic event is to an individual's identity and life narrative. This scale will be administered at baseline (before the first infusion) and again 3 weeks after the addition of WET. This scale will be used for exploratory analyses for Aim 3.

The **Impact of Event Scale-Revised (IES-R)** is one of the most widely used self-report measures of stress reactions to traumatic events,[67] measuring both intrusion and avoidance. Correlations between IES-R subscales and PTSD diagnosis assessed with the CAPS are high (>0.75). Unlike the PCL-5, this scale is able to assess changes in PTSD symptoms (intrusion and avoidance) over a 24-hour time period. In this study, we will use this measure as a secondary outcome measure to assess for rapid improvement in PTSD symptom severity at 24-hours after the first ketamine infusion, and to assess symptom change at each ketamine infusion and on the ketamine response assessment day.

The **Quick Inventory of Depressive Symptomatology – Self-Report (QIDS-SR)** is a commonly used self-report scale to assess depressive symptom severity.[66] The total score of the QIDS-SR is based on the nine criterion symptom domains of major depressive disorder. In this study, we will use this measure as a secondary outcome measure to assess for rapid improvement in comorbid depressive symptom severity at 24-hours after the first ketamine infusion, and to assess symptom change at each ketamine infusion and on the ketamine response assessment day.

The **Hood Mysticism Scale (HMS)** is a validated measure of subjective spirituality, tested in multiple cultural contexts.[79] More recently this scale has been used to capture mystical or spiritual experiences during sub-anesthetic ketamine infusions, and there is evidence that these mystical experiences under ketamine treatment may mediate treatment response, at least in alcohol use disorder populations.[80] In this study, we will use the 8-item version of this scale to assess mystical experiences for exploratory analyses of mediators of response to ketamine. This scale is administered immediately after the end of Infusions 1 and 2, as we expect participants' experiences to be more intense during the first two infusion days.

The **Psychological Insight Questionnaire (PIQ)** assesses insightful experiences, which may be an essential part of psychedelic treatments.[81] This newly developed questionnaire assess many aspects of psychological insight, including realizations about personality, relationships, emotions, and behaviors, with the goal of assessing these experiences in clinical trials of psychedelic medications. This scale will be administered at the end of the post-infusion monitoring period on Infusions 1 and 2, as we expect participants' experiences to be more intense during the first two infusion days.

The **Columbia Suicide Severity Rating Scale (C-SSRS)** is a comprehensive, semi-structured interview measure commonly employed in clinical trials. The C-SSRS measures the full spectrum of suicidality, including passive and active suicidal ideation, suicidal intent, and suicidal behaviors.[60] All study subjects will be assessed for suicidal ideation and behavior by the study PI or other trained member of the study team. Both past-month and lifetime versions of the C-SSRS will be administered at study screening. Individuals who score a 4 or greater on the past-month suicidal section, or who have engaged in any suicidal behavior in the past month, will be excluded and referred promptly for clinical care. Our clinicians and staff at the Depress Anxiety Center all undergo formal web-based training on administering the C-SSRS, and have extensive experience in its utilization. The Center has established SOPs for handling suicidality. For patients who do not show suicidality at the described threshold and proceed to participate in this study, the C-SSRS will be administered at each assessment time point (until 12 weeks, and then monthly up to 24 weeks or until loss of response), to assess for suicidal ideation and participant safety throughout the study. Participants with scores of 4 or greater at any point during the study will be exited from the study and promptly referred for clinical care.

The **Sheehan Disability Scale (SDS)** is a brief, 5-item self-report scale that assesses functional impairment in domains of work or school, social life, and family life.[59] Higher scores on this scale represent higher functional impairment. This scale will be administered at screening, and then at each assessment time point (weekly until 12 weeks, and then monthly up to 24 weeks or until loss of response).

The Clinical Global Impression –Severity and –Improvement scales (CGI-S and CGI-I) are among the most widely used brief assessment tools in psychiatry and clinical trials.[82] The CGI-S will be administered

at screening and baseline prior to any infusions, and both the CGI-S and the CGI-I will be administered at each assessment time point (weekly until 12 weeks, and then monthly up to 24 weeks or until loss of response) by the PI or another study clinician, to determine global severity of psychiatric illness.

The **Brief Psychiatric Rating Scale (BPRS)** is a clinician-administered assessment used to capture acute behavioral changes throughout treatment.[73] We will use only the four items assessing positive (+) symptoms of psychosis such as conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content for this proposed study. The scale will be administered before and after each infusion.

The **Clinician-Administered Dissociative States Scale (CADSS)** is commonly used in ketamine studies, and will be administered before and after each infusion to assess the severity of dissociative symptoms associated with ketamine administration.[72]

The **Young Mania Rating Scale (YMRS)**, first item (assessing elevated mood), is commonly used in ketamine studies.[74] We will administer only the first item of the YMRS before and after each infusion.

Online Extinction Learning Task: The computerized task, administered online, consists of three phases: an initial aversive conditioning phase (in context A), extinction learning phase (in context A), and further

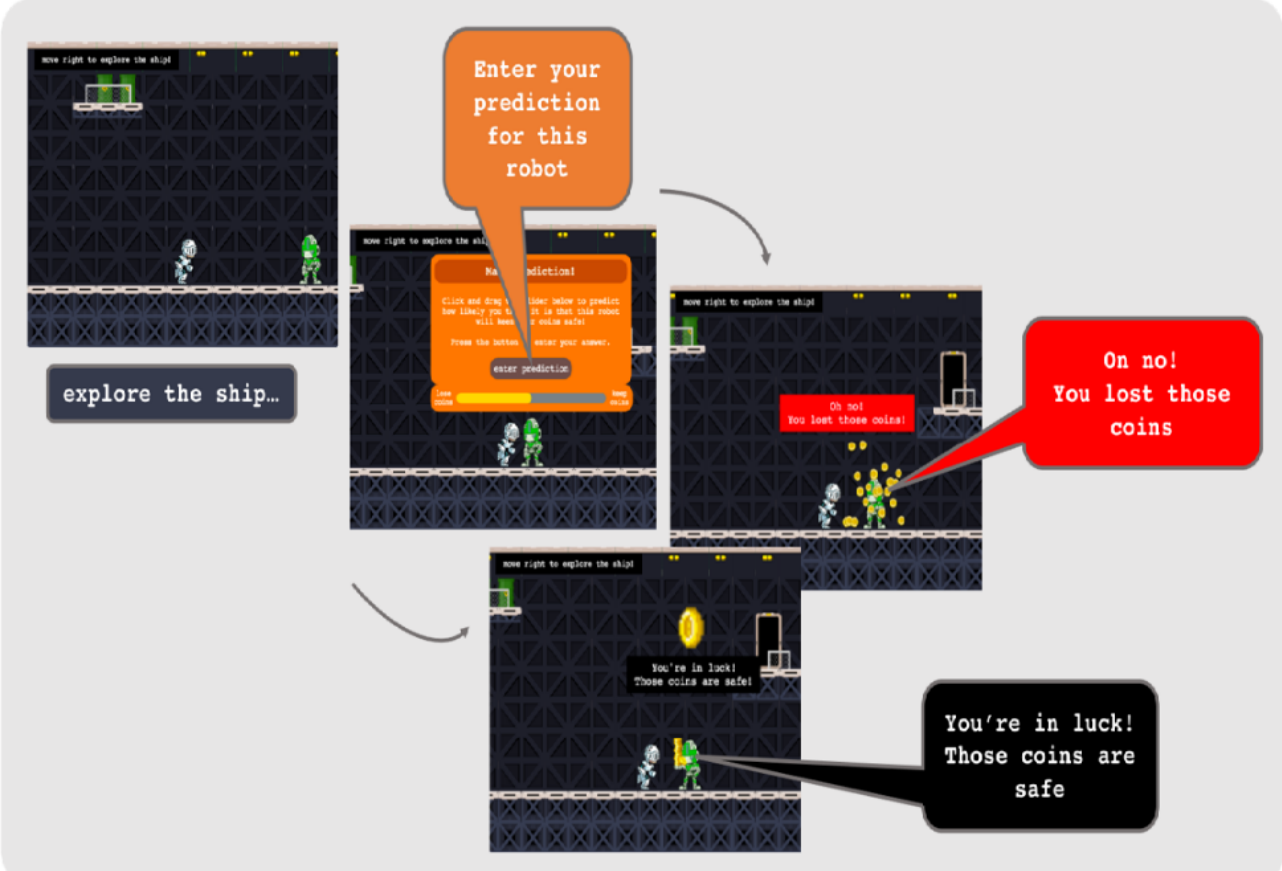


Figure 7. Online extinction learning task (updated version). Participants are told that they are traveling through different zones of a spaceship, and needed to escape with enough space coins to power their journey home. Unfortunately, the coins need to be carried by helper robots, some of whom are unreliable. On each trial, participants encounter a robot and rate how likely they think that robot will be to lose coins using a sliding bar (participants are informed that their ratings will not change the outcome they observe, but that their predictions should be as accurate as possible in order to aid future space travelers). In a second version of the task (identical in structure but with an underwater setting), participants must travel through different parts of the ocean, and predict how likely they think different sea creatures they encounter are to keep or lose pearls they must trade for their passage.

extinction learning (in novel context B) (see Figure 7). Importantly, the conditioned stimulus (CS) associated with the aversive loss outcome (US), the CS+, is only partially reinforced (P(US|CS+)=1/3), and the transition to extinction (P(US|CS+)=0) is unsignaled. This design maximizes uncertainty about whether CS+ trials during extinction should be grouped with unreinforced conditioning phase CS+ trials, implying a common cause is responsible for both kinds of observations, or instead that the change in contingencies indicates it is likely that a new cause is active in the environment. The predictive measure generated from this task for Aim 2 analyses (PTSD symptom change between baseline and 12 weeks from the start of WET) is the difference in discrimination between CS+ and CS- across the first six blocks of the task.

Further, loss expectancy ratings data from each trial of the online extinction task will be analyzed via a computational model of latent cause inference developed by Gershman, Niv, and colleagues[75,76] (see Data Analysis Strategy). There are two versions of the task (see description in Figure 7 note): one version will be administered prior to any ketamine infusions, and the second version after completion of the first four infusions. We will examine whether improvement in extinction learning from baseline to completion of four initial ketamine infusions (prior to starting WET) is associated with PTSD symptom improvement from baseline to 12 weeks from the start of WET.

8.2 SAFETY AND OTHER ASSESSMENTS

Participants in this proposed study will provide the following safety data:

(A) Data related to medical history, physical examination including review of systems, vital signs, ECG, routine laboratory tests (comprehensive metabolic panel, complete blood count, thyroid function testing) needed to determine eligibility and to monitor safety of participants
(B) Measures to assess for any acute side effects associated with ketamine before and after each infusion; potential longer- lasting side effects will be assessed weekly until resolution.

For laboratory tests, all results will be reviewed by the PI or study-affiliated psychiatrist, and any incidental finding will be conveyed to the subject with provision for additional work-up if needed.

Plasma ketamine and norketamine levels will be assessed via serial blood draws at the first ketamine infusion. Blood will be drawn from a second IV catheter at 30, 60, 90, and 120 minutes from the start of the infusion. Samples will be spun down and aliquoted into plasma samples. These samples will then be transported to Mount Sinai Clinical Laboratory Services (Sinai Labs) for shipment to an external laboratory (LabCorps) for the ketamine and norketamine levels.

The **Patient-Rated Inventory of Side Effects (PRISE)** Adverse Event Visit Checklist[71] is a clinician-administered questionnaire used to qualify side effects by identifying and evaluating the tolerability of each symptom. This scale will be completed before and after each infusion, and at each assessment time point (weekly until 12 weeks, and then monthly up to 24 weeks or until loss of response), by the PI or another study psychiatrist.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

All adverse events (AEs), defined as any physical or clinical change or disease experienced by a participant at any time during the course of the study, will be recorded in the participant's research records and will be captured in the electronic data capture system. Dr. Feder will be responsible for reporting to and following the guidance of any other applicable oversight bodies, including (but not limited to) the Institutional Review Board, the Data Safety and Monitoring Board.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the

study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

The PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Drs. Adriana Feder, James Murrough, Manish Jha, or Matthew Klein will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Dr. Feder will be responsible for reporting AEs to and following the guidance of any other applicable oversight bodies, including (but not limited to) the Institutional Review Board, the Data Safety and Monitoring Board, and the sponsor (the Icahn School of Medicine at Mount Sinai). At six-month intervals during the course of the study and again at its completion, the DSMB will be provided with summaries of the numbers and rates of adverse events. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.

Many subjects may admit to fleeting thoughts of death or briefly wishing for death; these thoughts need to be considered in context of the subject's overall history, along with a consideration of other risk factors for suicide. The presence of suicidal ideation without intent will therefore not be considered an Adverse Event, unless the suicidal ideation has increased in frequency or severity since baseline.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the DSMB and ISMMS IRB.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the DSMB or ISMMS IRB and should be provided as soon as possible.

The study sponsor (ISMMS) will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Both ketamine and WET have been extensively used in clinical trials and clinical practice, thus AEs associated with these treatments are known; they are summarized in the study consent form, and are reviewed with study participants during administration of study consent procedures. In the event that

any unexpected AE emerges during the course of the study, this unexpected AE will be added to the study consent (through an IRB amendment request), and reviewed with study participants during consent procedures.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.3.9 REPORTING OF PREGNANCY

In the event that a participant becomes pregnant while completing the study intervention(s), the participant will be exited from the trial after having completed end-of-infusion safety labs. Any pregnancies that occur while a subject is active in the protocol and after they have received ketamine infusions will be reported to the DSMB, ISMMS IRB, and other agencies (FDA, OHRP) as necessary.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- 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
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 5 business days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 6 months of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Unanticipated problems will be added to the study consent form if any are identified (via an IRB amendment). Newly enrolled participants will thus be informed about any such problems during administration of consent procedures for the study.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):
    - The primary outcome is change in PTSD symptom severity from baseline to 12 weeks from the start of WET measured by the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) score at 12 weeks from the start of WET minus the CAPS-5 score at baseline. The analysis of the primary endpoint for this pilot study will be descriptive and no formal hypothesis testing will be conducted. The mean change in CAPS-5 score and corresponding 95% confidence interval will be reported.
- Secondary Efficacy Endpoint(s) (Exploratory):

    In this early-phase study, analyses of secondary efficacy outcomes will be considered exploratory and hypothesis-generating. Therefore, no formal hypothesis testing will be conducted.

9.2 SAMPLE SIZE DETERMINATION

In this pilot study up to 15 patients will be enrolled. A sample size of 15 patients will produce a two-sided 95% confidence interval around the mean change in CAPS-5 at 12 weeks from the start of WET with a distance from the mean to the limits that is equal to 0.5 standard deviations.
Precision was calculated using PASS 2019.[83]

9.3 POPULATIONS FOR ANALYSES

Analysis datasets will include and Intention-to-treat (ITT) Analysis Dataset (all enrolled patients) and a Per-protocol Analysis Dataset (including only participants who completed the study). Additionally, a Safety Analysis Dataset and descriptive analyses will include all participants in the study.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Continuous variables will be summarized using the following descriptive statistics: number of non-missing values, means, standard deviations, medians, interquartile range, maximum, and minimum. Categorical variables will be summarized using number of non-missing values, counts and percentages.

Rates of events will be calculated as the ratio of the total number of events recorded divided by the total patient-time. Total patient-time will be calculated by summing the time (in study time units, e.g., days or months) that patients were at risk for a specific event from the reference time point until either study exit or the end of the time period of interest. Rates and their 95% confidence intervals will be reported.

Time-to-event variables will be summarized using the Kaplan-Meier method.

For any variable measured at multiple points in time, change since the day prior to starting WET, "pre-WET" (i.e., the day when response to ketamine is assessed), will be calculated as the difference between the value of the variable at a specific point in time (e.g. 12 weeks) minus the value from pre-WET. Relative change from pre-WET will be calculated as the value of a parameter at a specific point in time minus the pre-WET value of the parameter divided by the pre-WET value of the parameter. Percent change will be calculated as the relative change multiplied by 100.

Should any of the statistical methods proposed prove unsuitable during data analysis, more appropriate methods will be used. These include data transformation (for example to a logarithmic scale) to satisfy model assumptions such as normally distributed residuals with constant variance, the application of non-parametric techniques or the use of a different link function or analytical/modeling technique. The SAP will be updated with the methods used and the justification for the change prior to data set and database lock.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary outcome is change in PTSD symptom severity from baseline to 12 weeks from the start of WET measured by the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) score at 12 weeks from the start of WET minus the CAPS-5 score at baseline. The analysis of the primary endpoint for this pilot study will be descriptive. The mean change in CAPS-5 score from baseline with corresponding 95% confidence interval will be reported.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

- **<u>Secondary Efficacy Outcomes (Exploratory)</u>:** In this early-phase study, analyses of secondary efficacy outcomes will be considered exploratory and hypothesis-generating. CAPS-5, PCL-5, MADRS, CGI and SDS scores will be collected weekly through 6 weeks after the start of WET from all

eligible participants, and thereafter until 12 weeks (up to weekly, as tolerated, ensuring assessment at the 12-week time point for all participants). All participants will be followed naturalistically for 12 weeks from the start of WET, in order to capture, descriptively, more gradual effects of WET and potential effects of the combination of ketamine + WET in all patients. Thereafter, they will be collected monthly through week 24 from start of WET or until loss of treatment response, for the subgroup of participants who demonstrate improvement on the CAPS-5 at the 12-week assessment. Aggregate scores prior to adding WET, during WET, and during the maintenance phase (weeks 3 onward) will be reported descriptively at each time point using the number observed, mean, standard deviation, median, and interquartile range. Individual patient trajectories on these measures will be plotted over time to explore treatment response and patterns in maintenance of response. Mean change in CAPS-5 scores from baseline and corresponding 95% confidence intervals, as well as the proportion of patients with ≥30% improvement from baseline on the CAPS-5 will also be reported at each time point. In addition, linear mixed-effects models of these outcomes may be fit to compare mean scores over time. Mixed models will test for the inclusion of a random intercept for patient and fixed effects for week against a fixed intercept model using a likelihood ratio test after comparing each model fit statistic (i.e., Akaike information criterion, AIC) where the best fitting model is the model with the lowest corresponding AIC. Once fit is assessed, parameter interpretation will commence.

- **IES-R and QIDS-SR with past-24-hour recall** – collected only at baseline, before each ketamine infusion, 24 hours after the first infusion, and on the response to ketamine assessment day – will be examined descriptively.

The relationship between depressive symptoms and PTSD will be explored to assess whether worsening depressive symptoms correlate with worsening PTSD symptoms and whether there is any evidence that the worsening of one precedes the other. Scale scores of both measures will be plotted over time together to evaluate trends descriptively. Fixed and mixed effects regression models will also be explored to estimate effects and 95% confidence intervals.

- Finally, additional analyses might explore differences with a historical comparison group from our published repeated IV ketamine study for PTSD (Feder et al 2021).

Aim 2 (Exploratory): To evaluate whether ketamine-induced change in extinction learning predicts maintenance of ketamine response over time. We will use regression models to evaluate whether ketamine-induced change in extinction learning [improvement in extinction learning between two time points: *(1)* before infusions and *(2)* after four infusions (prior to starting WET), measured with the computerized online Extinction Learning Task, is associated with change in CAPS-5 at 12 weeks after the start of WET. A univariable model of ketamine-induced change on the extinction learning measure [discrimination between aversively conditioned (CS+) and safe (CS-) stimuli over the first six blocks of the task] and changes in CAPS-5 score will be examined. Beta coefficients and 95% confidence intervals will be reported. A significant association between greater ketamine-induced improvement in extinction learning and improvement in CAPS-5 scores will be considered supportive of Hypothesis 2.

***Computational analyses*:** Loss expectancy ratings data from each trial of the online extinction task will be analyzed via a computational model of latent cause inference developed by Gershman, Niv, and colleagues.[75,76] Importantly, this model has previously been shown to be able to explain individual differences in failure of extinction learning in both healthy volunteers and trauma-exposed individuals

with and without PTSD.[75,76] In brief, the model posits that during learning, an individual attempts to infer which underlying (latent) cause is responsible for their observations, based on a combination of their previous experience and prior beliefs about causal structure of the environment. Prior beliefs about the causal complexity of the environment are governed by a single concentration parameter, alpha (α). The key model output submitted to further analysis is the likelihood for each participant of a model where α was allowed to be > 0 (favoring multiple causes), compared to a model where α=0 (single cause responsible for all observations), quantified as a log Bayes Factor (logBF; higher values=greater likelihood of a multi-cause model). The analysis will be run in MATLAB,[84] using publicly-available code associated with Gershman and Niv's published work.[75,76]

9.4.4 SAFETY ANALYSES

Side effects measured by the Patient-Rated Inventory of Side Effects (PRISE) will be reported descriptively using the number and percentage of patients with each reported side effect. Psychotomimetic, dissociative, and manic symptoms experienced on infusion days, measured by the Clinician-Administered Dissociative States Scale (CADSS), the Brief Psychiatric Rating Scale (BPRS), and the first item (elevated mood) of the Young Mania Rating Scale (YMRS) will also be reported descriptively. The distribution of suicide risk (low, moderate or high) as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS) will be reported by visit descriptively.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Patient demographics and baseline characteristics will be summarized using mean and standard deviation or median and interquartile range as appropriate for continuous measures, and number and percentage for categorical measures.

9.4.6 PLANNED INTERIM ANALYSES

Not applicable.

9.4.7 SUB-GROUP ANALYSES

Not applicable.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Not applicable.

9.4.9 EXPLORATORY ANALYSES

Secondary efficacy endpoint analyses and Aim 2 analyses are exploratory (see details above).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written or electronic documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol: HRP-502a, documentation of informed consent.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

After completing the screening process at DAC through protocol STUDY-10-00606, potentially eligible participants will be invited to participate in a screening visit for this protocol. Informed consent may be obtained in person or remotely, using a HIPAA-compliant telehealth platform(e.g., VSee, Doximity, HIPAA-Zoom) and the electronic consent survey housed on REDCap. As the proposed study involves ketamine infusions, the informed consent will be obtained by either the PI or one of the study-affiliated psychiatrists. Consent may be obtained by a clinical research coordinator prior to administering clinical rating scales, self-report scales, the extinction learning task, and/or the medical clearance assessment. In this case, the PI or study-affiliated psychiatrist will re-review the consent form with the participant and will co-sign the form prior to the participant beginning the first study intervention (ketamine infusions). Potential participants will be informed about possible alternatives to participating in the study. A release of information will be obtained for review of any available historical and clinical data. Authorization is also obtained from each subject in the consent document, permitting the research team to use, create, or disclose the subject's PHI for research purposes. The nature of the project, procedures, relative risks and benefits, and alternatives to participation in the project will be discussed with the individual. The individual will be given ample opportunity to ask any questions they might have. Following this discussion, the individual will be given a physical or electronic copy of the consent form to review at their leisure, and any remaining questions will be answered. If the individual remains interested in the project, written or electronic informed consent is obtained, and medical and psychiatric screening procedures are undertaken to confirm eligibility. If the individual decides not to participate in this study, a staff member provides reasonable and timely assistance in obtaining an alternative referral, if so desired. The decision not to participate does not affect eligibility to participate in future studies, to receive treatment at Mount Sinai or at any program serving PTSD populations, or to receive treatment on a private basis. Subjects will be also be given the opportunity to withdraw from the study at any point. The consent process also includes documentation of permission to obtain previous medical records, including contact with previous physicians, pharmacies, and family members.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will

promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible. Prior to beginning any study procedures conducted remotely via HIPAA-compliant telehealth video platform (e.g., clinical assessment, delivery of a WET session), study personnel will first confirm with the participant that he/she is situated in a private room at home, with no other persons present in the room, to ensure privacy and confidentiality.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the ISMMS. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site and by ISMMS research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the ISMMS.

Certificate of Confidentiality

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the ISMMS.
Blood samples will be collected for routine clinical labs at screening (medical clearance) and study exit, and to measure plasma ketamine and norketamine during the first ketamine infusion. No specimens will be stored for future use.

When the study is completed, access to de-identified study data should requested by contacting the PI, Dr. Feder.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**MSSM Additional Monitor**
Adriana Feder, Associate Professor of Psychiatry	*James Murrough, Assistant Professor of Psychiatry*
Icahn School of Medicine at Mount Sinai	*Icahn School of Medicine at Mount Sinai*
1 Gustave L. Levy Place, Box 1230, New York, NY 10029	*1 Gustave L. Levy Place, Box 1230, New York, NY 10029*
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Adriana.feder@mssm.edu	*James.murrough@mssm.edu*

10.1.6 SAFETY OVERSIGHT

Study PI Dr. Feder will monitor potential risks and oversee protection against risks on a regular basis, working closely with Co-Is Drs. Jha and Murrough for the duration of the study. The study team will also meet weekly as part of the larger weekly group meetings at our Depression and Anxiety Center for Discovery and Treatment (DAC) at Mount Sinai, where the proposed study will be conducted. All adverse events (AEs), defined as any physical or clinical change or disease experienced by a participant at any time during the course of the study, will be recorded in the participant's research records and will be captured in the electronic data capture system. Dr. Feder will be responsible for reporting to and following the guidance of any other applicable oversight bodies, including (but not limited to) the Institutional Review Board and the Data Safety and Monitoring Board.

Dr. Feder and the full-time study coordinator will evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome.

A Data and Safety Monitoring Board (DSMB) has been established as an independent body to ensure the safety of participants and the validity and integrity of study data for all protocols at DAC that involve ketamine administration.

Functions of the Data and Safety Monitoring Board (DSMB)

The primary goals of the DSMB are as follows:

1. To monitor and advise on scientific and ethical issues related to study implementation for the protection of human subjects.
2. To review and approve the protocol and subsequently conduct bi-annual reviews to determine whether participant safety has been adequately safeguarded.
3. To review procedures and decisions regarding the adequate protection of specific patients when investigators remove patients from protocol treatment because of serious adverse events (SAEs) or clinical deterioration.
4. To review progress to see that enrolment and retention goals are being met.
5. To monitor and advise on ethical issues related to serious adverse events.
6. To oversee the confidentiality of data, and quality of data collection, management, and analysis.
7. To conduct any interim analysis of study outcome, as well as determining from such analyses whether study continuation or discontinuation is warranted.

Membership of the DSMB

The DSMB will be the same DSMB that currently reviews all ongoing ketamine clinical trials conducted by investigators at DAC, and will be comprised of the same personnel. The DSMB includes the following members: Dan Iosifescu, MD (DSMB Chair, Department of Psychiatry, New York University), Lee Chang, MD (Department of Anesthesiology, Baylor College of Medicine), Mark Green, MD (Department of Neurology, Icahn School of Medicine at Mount Sinai), Menachem Wiener, MD (Department of Anesthesiology, Icahn School of Medicine at Mount Sinai), and Emilia Bagiella (Statistician, Icahn School of Medicine at Mount Sinai). The board will review the project's data and safety on bi-annual basis and report their findings to the PI. Dr. Feder will work with the study research coordinator to convene the DSMB within the first three months of the project period.

Monitoring of Safety Data by the DSMB

Safety Reporting to the DSMB. The DSMB review adverse events (AEs and serious adverse events [SAEs]), as well as treatment retention rates and reasons for dropout.

Serious Adverse Events. Expedited review will occur for all Serious Adverse Events (SAEs) – any fatal event, immediately life-threatening event, permanently or substantially disabling event, or any event requiring inpatient hospitalization. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. Notification by email, and fax transmittal of all related study forms shall be made to the DSMB within 2 days of the occurrence of any SAE. Additional reporting to the Mount Sinai IRB will be done within 24 hours of the SAE.

Non-Serious Adverse Events. At six-month intervals during the course of the study and again at its completion, the DSMB will be provided with summaries of the numbers and rates of adverse events. These reports will include types of events, severity, and treatment phase. Data on individual non-serious adverse events is not expected to be needed for this review.

Other Safety-Related Reports. At six-monthly intervals throughout the course of the study, the DSMB will also receive summary reports of treatment retention and reasons for dropout, by study phase.

Study Stopping Rules. If at any time during the course of the study, the DSMB judges that risk to participants outweighs potential benefits, the DSMB shall have the discretion and responsibility to recommend terminating the study.

DSMB Monitoring of Data Quality. At least half-yearly during the course of the study, the DSMB will receive a report on data quality and completeness. At a minimum, this will include an overview of the progress of participant recruitment and retention; summary reports describing patient compliance with WET; and a summary of the completeness and quality of key data elements needed to characterize patients, and their primary and secondary outcomes. These reports will be used by the DSMB to evaluate the capacity of the data capture and processing to support scientifically valid analyses.

Biannual DSMB Report to the IRB. Biannually during the course of the study the DSMB will prepare a summary report of its findings regarding safety and quality based on data received to that point in the study. This report will include a summary of all safety findings as well as an assessment of protocol compliance and data quality. Any recommendations to improve patient safety, protocol adherence, or data quality will be made in the annual DSMB report. A copy of the annual DSMB report will be sent to the Mount Sinai IRB along with the annual renewal report.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- On-site monitoring will be conducted by the database manager for the study monthly throughout the study, comprehensively reviewing all CRF's and eCRF's for completion and accuracy. At study close, the database manager will randomly review 10% of cases to verify completion and accuracy of all CRF's and eCRF's for a given participant. The results of these audits will be available within the electronic data capture system, REDCap, and will be summarized to the PI.
- Independent audits will not be conducted.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the PI for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the PI and Co-I Dr. James Murrough will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all source data/documents and reports for the purpose of monitoring and auditing by the ISMMS, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by the ISMMS. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and record any deviations from the IRB-approved protocol. All deviations must be addressed in study source documents. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested by other researchers 10 years after the completion of the primary endpoint by contacting Dr. Adriana Feder or Dr. James Murrough.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the ISMMS FCOI Committee has established policies and procedures for

all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable.

10.3 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISMMS	Icahn School of Medicine at Mount Sinai
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MDD	Major Depressive Disorder
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator

PTSD	Posttraumatic Stress Disorder
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
WET	Written Exposure Therapy
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
1.1	3/23/21	Limited maximum dose of ketamine to 60 mg per infusion (dose for approximately 120 kg body weight)	Safety; requested by FDA
1.2	5/24/21	Removed End of Infusions Medical Assessment and changed CAPS-5 cutoff score from (score ≥ 25) to (score ≥ 30).	Undue patient burden; not necessary for patient safety For consistency with prior studies, and to capture moderate severity PTSD
2.0	6/23/21	All eligible participants will receive six (6) infusions of ketamine and five (5) WET sessions, regardless of responder status, and will be assessed weekly for 12 weeks following the start of WET. After 12 weeks, participants who demonstrate ≥ 30% improvement at the 12-week assessment will be assessed monthly for up to 24 weeks following the start of WET or until loss of response. Adding Hood Mysticism Scale and Psychological Insight Questionnaires to Infusions 1 and 2.	Based on our recent meeting with a panel of experts in the field, and following their recommendation, we would like to offer all 6 infusions and 5 WET sessions in order to capture more gradual effects of WET and the potential effects of Ketamine + WET in both responders and non-responders to ketamine. The primary aim of the study remains unchanged. We are adding the scales to assess participant experiences during the infusions.

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